March / April 2021
Volume 50, Number 2

Applied Radiology

50 YEARS

The Journal of Practical Medical Imaging and Management

Still Growing at 50

Applied Radiology's publisher shares his thoughts and reflections as the journal marks its 50th year of covering the field of medical imaging.

SA-CME Acquired Pericardial Pathologies: Imaging Features, Clinical Significance, and Management

Imaging Findings in the Setting of Rhabdomyolysis

Eye on AI: A Call for Radiology-led Innovation

Pediatric Radiological Case: Alveolar Capillary Dysplasia with Misalignment of Pulmonary Veins

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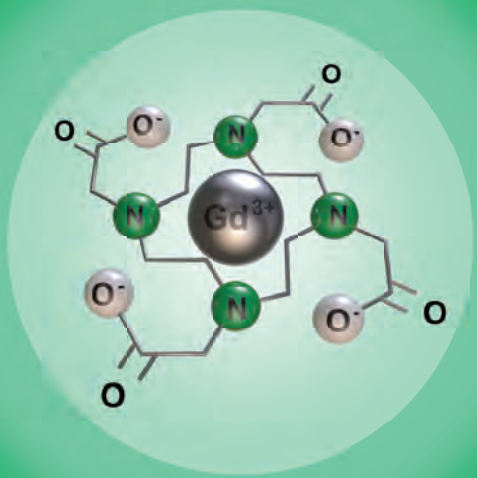

Clariscan™ — a trusted macrocyclic molecule from the world's leading contrast media company

Clariscan™
(gadoterate meglumine)
injection for intravenous use

We understand changing from the status quo is hard, particularly in these uncertain times. We understand that you want stability in your supply and in your manufacturer, as well as in your GBCA.

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Company — GE Healthcare has been meeting the contrast media needs of US radiology departments for over 40 years, with a comprehensive portfolio across X-ray/CT, MRI, and Ultrasound.

Stability. Reliability. Value.

Latest updates!

- **Clariscan now has pre-filled syringes and Pharmacy Bulk Pack available to help with workflow and convenience**
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IMPORTANT SAFETY INFORMATION ABOUT CLARISCAN™

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF) Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle, and internal organs.

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR <30 mL/min/1.73 m²), or**
  - **Acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**
- **For patients at highest risk for NSF, do not exceed the recommended Clariscan dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.**

Please see additional Important Safety Information on the following pages and how to access the Full Prescribing Information.

References:

1. Port M et al. *Biometals.* 2008; 21(4):469-90.
2. Tweedle MF et al. *App Radiol.* 2014; (Suppl.):1-11.
3. Data on file. GE Healthcare Investment.

PRODUCT INDICATIONS AND USE:

CLARISCAN™ (gadoterate meglumine) is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine, and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

IMPORTANT SAFETY INFORMATION ABOUT CLARISCAN™

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle, and internal organs.

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- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**
- **For patients at highest risk for NSF, do not exceed the recommended Clariscan dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.**

Contraindications

History of clinically important hypersensitivity reactions to Clariscan.

Warnings and precautions

- **Nephrogenic Systemic Fibrosis (NSF):**
  - NSF has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeat dosing appear to increase the risk.
- **Hypersensitivity reactions:**
  - Anaphylactic and anaphylactoid reactions have been reported with gadoterate meglumine, involving cardiovascular, respiratory, and/or cutaneous manifestations. Some patients experienced circulatory collapse and died. In most cases, initial symptoms occurred within minutes of gadoterate meglumine administration and resolved with prompt emergency treatment.
  - Before Clariscan administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to Clariscan.
  - Administer Clariscan only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.
- **Gadolinium retention:**
  - Gadolinium is retained for months or years in several organs. The highest concentrations have been identified in the bone, followed by brain, skin, kidney, liver and spleen. The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs.
  - Consequences of gadolinium retention in the brain have not been established. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention.
- **Acute kidney injury:**
  - In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging.
- **Extravasation and injection site reactions:**
  - Ensure catheter and venous patency before the injection of Clariscan. Extravasation into tissues during Clariscan administration may result in tissue irritation.
- **Pre-filled syringes must not be frozen. Frozen syringes should be discarded.**

Pharmacy Bulk Package Preparation:

- Do not use the Pharmacy Bulk Package for direct intravenous infusion.
- Do not use if tamper-evident ring is broken or missing.
- Perform the transfer of Clariscan from the Pharmacy Bulk Package in an aseptic work area, such as laminar flow hood and using aseptic technique and suitable transfer device. Penetrate the closure only one time.
- Once the container closure is punctured, do not remove the Pharmacy Bulk Package from the aseptic work area.
- The Pharmacy Bulk Package is used as a multiple dose container with an appropriate transfer device for filling empty sterile syringes.
- Use each individual dose of Clariscan promptly following withdrawal from the Pharmacy Bulk Package.
- Use the contents of the Pharmacy Bulk Package within 24 hours after initial puncture.

Adverse reactions

- The most common adverse reactions (≥ 0.2%) associated with gadoterate meglumine in clinical trials were nausea, headache, injection site pain, injection site coldness and rash.
- Serious adverse reactions in the postmarketing experience have been reported with gadoterate meglumine. These serious adverse reactions include but are not limited to: arrhythmia, cardiac arrest, respiratory arrest, pharyngeal edema, laryngospasm, bronchospasm, coma and convulsion.

Use in specific populations

- **Pregnancy:** Because of the potential risks of gadolinium to the fetus, use Clariscan only if imaging is essential during pregnancy and cannot be delayed. Advise pregnant women of the potential risk of fetal exposure to GBCAs.
- **Lactation:** While no data is available for gadoterate meglumine, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is present in breast milk.
- **Pediatric Use:** The safety and efficacy of gadoterate meglumine at a single dose of 0.1 mmol/kg have been established in pediatric patients from birth (term neonates ≥ 37 weeks gestational age) to 17 years of age based on clinical data in 133 pediatric patients 2 years of age and older, and clinical data in 52 pediatric patients birth to less than 2 years of age that supported extrapolation from adult data. Safety of gadoterate meglumine has not been established in preterm neonates.

Please see Full Prescribing Information for Clariscan, including Boxed Warning and Medication Guide, for additional important safety information. Visit https://www.gehealthcare.com/-/jssmedia/a4f1c1c8f50d489387bf91292dba5629.pdf to access the Full Prescribing information.

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 800-654-0118 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION FOR CLARISCAN™ (gadoterate meglumine) Injection for Intravenous Use

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle, and internal organs.

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR < 30 mL/ min/1.73 m^2), or**
  - **Acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing**
- **For patients at highest risk for NSF, do not exceed the recommended Clariscan dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration**

INDICATIONS AND USAGE

Clariscan is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier and/or abnormal vascularity.

CONTRAINDICATIONS

History of clinically important hypersensitivity reactions to Clariscan.

WARNINGS AND PRECAUTIONS

Nephrogenic Systemic Fibrosis Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73 m^2) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30 - 59 mL/min /1.73 m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60 - 89 mL/ min/1.73 m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle, and internal organs. **Report any diagnosis of NSF following Clariscan administration to GE Healthcare at (1-800-654-0118) or FDA at (1-800FDA-1088 or www.fda.gov/medwatch)**. Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid
(over hours to days), and usually reversible, decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (e.g., age > 60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing. The factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA, and the degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. For patients at highest risk for NSF, do not exceed the recommended Clariscan dose and allow a sufficient period of time for elimination of the drug prior to re-administration. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown.

Hypersensitivity Reactions Anaphylactic and anaphylactoid reactions have been reported with gadoterate meglumine, involving cardiovascular, respiratory, and/or cutaneous manifestations. Some patients experienced circulatory collapse and died. In most cases, initial symptoms occurred within minutes of gadoterate meglumine administration and resolved with prompt emergency treatment.

- Before Clariscan administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to Clariscan.
- Administer Clariscan only in situations where trained personnel and therapies are promptly available for treatment of hypersensitivity reactions, including personnel trained in resuscitation.
- During and following Clariscan administration, observe patients for signs and symptoms of hypersensitivity reactions.

Gadolinium Retention Gadolinium is retained for months or years in several organs. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (e.g. brain, skin, kidney, liver and spleen). The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs. At equivalent doses, gadolinium retention varies among the linear agents with Omniscan (gadodiamide) and Optimark (gadoversetamide) causing greater retention than other linear agents [Eovist (gadoxetate disodium), Magnevist (gadopentetate dimeglumine), MultiHance (gadobenate dimeglumine)]. Retention is lowest and similar among the macrocyclic GBCAs [Clariscan (gadoterate meglumine), Dotarem (gadoterate meglumine), Gadavist (gadobutrol), ProHance (gadoteridol)]. Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of GBCA administration and retention in skin and other organs have been established in patients with impaired renal function. There are rare reports of pathologic skin changes in patients with normal renal function. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention. While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring multiple lifetime doses, pregnant and pediatric patients, and patients with inflammatory conditions. Consider the retention characteristics of the agent when choosing a GBCA for these patients. Minimize repetitive GBCA imaging studies, particularly closely spaced studies when possible.

Acute Kidney Injury In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging. Screen all patients for renal impairment by obtaining a history and/or laboratory tests. Consider follow-up renal function assessments for patients with a history of renal dysfunction.

Extravasation and Injection Site Reactions Ensure catheter and venous patency before the injection of Clariscan. Extravasation into tissues during Clariscan administration may result in tissue irritation.

ADVERSE REACTIONS

GBCAs have been associated with a risk for NSF. Confirmed diagnosis of NSF has not been reported in patients with a clear history of exposure to gadoterate meglumine alone. Hypersensitivity reactions and acute kidney injury are described in other sections of the labeling.

- o The most common adverse reactions (≥ 0.2%) associated with gadoterate meglumine in clinical trials were nausea, headache, injection site pain, injection site coldness and rash.
- o Serious adverse reactions in the postmarketing experience have been reported with gadoterate meglumine. These include but are not limited to: arrhythmia, cardiac arrest, respiratory arrest, pharyngeal edema, laryngospasm, bronchospasm, coma and convulsion.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Because of the potential risks of gadolinium to the fetus, use Clariscan only if imaging is essential during pregnancy and cannot be delayed. Advise pregnant women of the potential risk of fetal exposure to GBCAs.
- **Lactation:** While no data is available for gadoterate meglumine, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is present in breast milk.
- **Pediatric Use:** The safety and efficacy of gadoterate meglumine at a single dose of 0.1 mmol/kg have been established in pediatric patients from birth (term neonates ≥ 37 weeks gestational age) to 17 years of age. Safety of gadoterate meglumine has not been established in preterm neonates.
- **Geriatric Use:** In clinical studies of gadoterate meglumine no overall differences in safety or efficacy were observed between these subjects and younger subjects. In general, use of Clariscan in elderly patients should be cautious, reflecting the greater frequency of impaired renal function and concomitant disease or other drug therapy. No age-related dosage adjustment is necessary.
- **Renal Impairment:** No Clariscan dosage adjustment is recommended for patients with renal impairment. Gadoterate meglumine can be removed from the body by hemodialysis.

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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February 2021 JB00834US

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The Journal of Practical Medical Imaging and Management

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March–April 2021 | Vol. 50, No. 2

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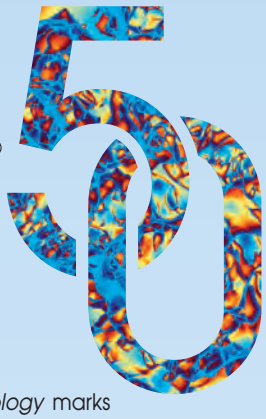

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Applied Radiology *(ISSN 0160-9963, USPS 943180) is published in print 6 times a year, January, March, May, July, September, and November, by Anderson Publishing Ltd at 180 Glenside Ave., Scotch Plains NJ 07076. Periodicals postage paid at Scotch Plains, NJ and additional mailing offices. Free subscriptions for US-based qualified radiology professionals. Subscriptions for the US and its territories and possessions: $115 per year, $225 for two years. Foreign and Canadian subscriptions $215 for one year payable in US funds, international money orders, or by credit card only. Postmaster: Please send address changes to Applied Radiology, PO Box 317, Lincolnshire, IL 60069-0317 (847-564-5942) or email AppliedRadiology@Omeda.com.*

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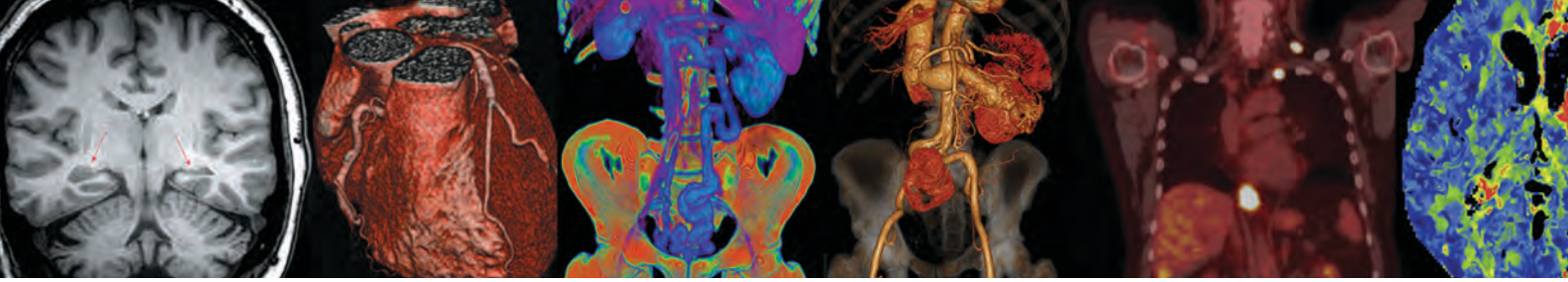


AppliedRadiology®

Still Growing at 50

As I sat down to compose this editorial to mark the start of *Applied Radiology's* 50th year of publication, the thought occurred to me that I, too, have just turned 50. I was just your typical mischief-making kid in grade school when my father, O Oliver Anderson, began managing the journal for Romain Pierson Publishing, in the 1980s. I was just out of high school when he acquired *Applied Radiology* for his own budding publishing company.

So, in many respects, I can say I've grown up with *Applied Radiology.*

I still remember attending the RSNA and so many other radiology conferences with my parents in those early days. I would manage the booth while he and my mother, Brenda, hiked the exhibit halls, networking with the physicians and vendors. What stood out to me then is that so many of you would stop by the booth to thank us for publishing a journal just for the radiology community.

Many of you still stop by the booth today, and your gratitude continues to remind us that *Applied Radiology* still matters—very much so.

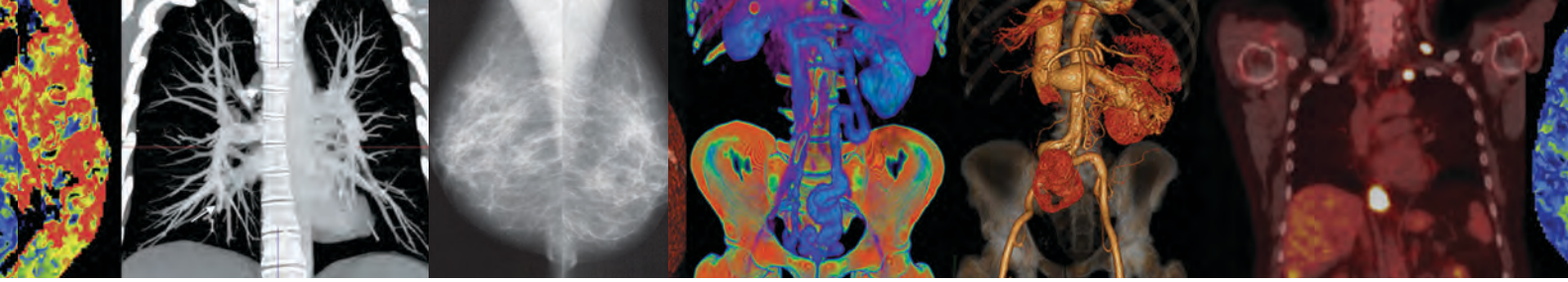
Yet none of this would be here today if it weren't for those individuals who not only believed in the need for a publication like *Applied Radiology,* but were also willing to step up and help us make it the best possible journal to meet the practical needs of medical imaging clinicians and professionals everywhere.

They were people like Dr Byron Gilliam (Gil) Brogdon, *Applied Radiology*'s first Editor-in-Chief. I never had the pleasure of meeting Gil, but I am told he was an amazing doctor and human being. Gil's career spanned more than six decades, and he was known to many as the 'Godfather of Forensic Radiology.' His textbook, "Forensic Radiology," remains a valuable resource for radiologists and researchers to this day. We still cherish his wit and humorous approach to writing and editing.

And then there was Dr Theodore (Ted) Keats, who by all accounts was the ideal successor to Dr Brogdon. A lover of life, music, the arts, and radiology (of course), Ted spent most of his career at the University of Virginia, where he was the Chairman of Radiology for 28 years. He is perhaps best known for one of his nine textbooks, "An Atlas of Normal Roentgen Variants That May Stimulate Disease," said to be the book most stolen from any radiology department anywhere. Ted brought to *Applied Radiology* a fresh mix of content for radiologists practicing in then-emerging

O Oliver and Brenda Anderson

Dr William (Bill) Bradley



Dr Byron Gilliam (Gil) Brogdon

Dr Theodore (Ted) Keats

Dr Stuart (Stu) Mirvis

Dr Erin Simon Schwartz

specialties like computed tomography and magnetic resonance imaging.

And who among us can forget Dr Stuart (Stu) Mirvis, who took over from Dr Keats at the turn of the 21st century? Stu had worked under Dr Keats at the University of Virginia, and he both recognized and appreciated *Applied Radiology* and the void it filled in the literature. Like Drs Brogdon and Keats, Stu had quite the way with words, penning more than 80 (mostly) tongue-in-cheek editorials under titles ranging from "Care and Feeding of a Visiting Professor," to "I Used to Interpret Images for a Living."

Stu's love for his colleagues and the profession shone brightly in his accounts of the radiology work life. During his 20-year tenure with us, Stu steered *Applied Radiology* through such challenging developments as the digital and internet revolution. Indeed, it would be an understatement to say that Stu played a major role in ensuring that *Applied Radiology* didn't just survive, but thrived, during a time when most print publications seemed to be dying a slow, painful death at the hands of open access journals and websites.

Important as the role these editorial leaders have played in our progress, so too is the role many of you have played in fostering the growth of *Applied Radiology*. Our family has had the tremendous pleasure of working closely with so many great people over the years, and we have formed lifelong friendships with many.

Some of our fondest memories include working with young residents and fellows in the programs we hosted for imaging companies (some of which the journal has outlived!) to encourage careers in research and academia. Many of those participants now lead radiology departments around the world, are sought-after speakers on the lecture circuit, and radiologic luminaries in their own right.

But none were more luminary than the late Dr William (Bill) Bradley. I recall his wonderful interactions with the trainees in our programs, as well as the annual dinners we enjoyed at RSNA with Bill and wife, Dr Rosalind Dietrich. It is these individuals, and the many wonderful people in the radiology-associated industries, who have made this journey so enjoyable over the years for my family.

And today we continue our journey into the future.

Editor-in-Chief Dr Erin Simon Schwartz, successor to Stu Mirvis, brings to the job unparalleled enthusiasm for taking *Applied Radiology* to the next level. Drawing on her many strong relationships with today's thought leaders, Erin and our team are strategically charting the course forward in our continuing pursuit to be your most trusted source of practical and actionable radiologic content.

You will see their plan begin to unfold over the course of this Golden Anniversary year, and I promise you, it is nothing short of audacious.

In closing, I want you all to know that it is not just our great honor to be part of the *Applied Radiology* journey. It is an even greater honor to have all of you along for the ride.

Here's to 50 more years!

Kieran N Anderson
Publisher

Celebrating 50 Years of *Applied Radiology*

Erin Simon Schwartz, MD, FACR

"…behind that glossy, black cover you will continue to find the same high-quality content you have come to expect from Applied Radiology*."*

A hearty congratulations to Oliver, Brenda, and Kieran Anderson, and their entire team, on the publication of this year's 50th volume of *Applied Radiology*!

It was with the April/May issue of 1972 that the journal, which back then labeled itself "The Journal of Radiologic Technique," was launched to widespread welcome from the medical imaging community.

So it is fitting that we begin our celebration now, with the March/April issue sporting the first and most visible of several updates we expect to roll out over the course of 2021.

Have you seen our new cover? If you only read the digital version, you may have plunged right into the content and missed it. I invite you to take a look. We are proud to introduce a striking new design of our cover and refresh of our logo. Both are sleek, both are unmistakably identifiable, and both present a distinctive complement to the beautiful imagery in *Applied Radiology*.

We believe these changes, and those still to come, vividly reflect our renewed and ongoing dedication to remain "*The* Journal of Practical Medical Imaging and Management" for every radiologist and affiliated imaging professional.

We hope that you appreciate our new look, but we also recognize that change can take time for some to get used to. But rest assured, behind that glossy, black cover you will continue to find the same high-quality content you have come to expect from *Applied Radiology*.

In closing, I invite you to join us in this and subsequent issues as we reflect on the past 50 years of *Applied Radiology* and its part in communicating the vital role that medical imaging plays in health care. These reflections, these expressions of our founding principles, will help us set the course for the next 50 years.

To paraphrase Winston Churchill, who famously said, "Those that fail to learn from history are doomed to repeat it," I would like to say without reservation that we have learned from our history, and we are determined to repeat all of its successes in the years to come.

Please join me in welcoming **Maddy C Artunduaga, MD,** of the University of Texas, Southwestern, to the Pediatric Radiology section of our Editorial Advisory Board. Maddy brings a wealth of experience in pediatric imaging with a special interest in genitourinary disorders, and we are very pleased to have her on our team.

Dr. Schwartz is the Editor-in-Chief of Applied Radiology. *She is the Chief of the Division of Neuroradiology and holds the Robert A Zimmerman Chair in Pediatric Neuroradiology in the Department of Radiology at The Children's Hospital of Philadelphia. She is also an Associate Professor of Radiology, Perelman School of Medicine, University of Pennsylvania. She can be reached at erin@appliedradiology.com.*

SA–CME Information

Acquired Pericardial Pathologies: Imaging Features, Clinical Significance, and Management

Description

There are several acquired diseases involving the pericardium. The clinical signs and symptoms of most of the pericardial disease are similar. This underscores the importance of medical imaging in identification of specific pericardial diseases.

Unfortunately, there are also similarities between the imaging features of several pericardial diseases. Therefore, familiarity with imaging features of different pericardial diseases is very important in the proper management of these patients. It is also of great importance that radiologists understand the clinical significance and management of different pericardial diseases so that they can better communicate with referring clinicians.

Learning Objectives

Upon completing this activity, the reader should be able to:

- Better characterize different pericardial pathologies using available imaging modalities.
- Explain the clinical significance of different acquired pericardial diseases.
- Outline the steps in the management of the more common pericardial pathologies.

Accreditation/Designation Statement

The Institute for Advanced Medical Education is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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Target Audience

- Radiologists
- Related Imaging Professionals

System Requirements

In order to complete this program, you must have a computer with a recently updated browser and a printer. For assistance accessing this course online or printing a certificate, email *CustomerService@AppliedRadiology.org*.

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Date of release and review: **March 1, 2021**
Expiration date: **February 28, 2023**

Disclosures

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Acquired Pericardial Pathologies: Imaging Features, Clinical Significance, and Management

Pegah Khoshpouri, MD; Mahdie Hosseini, MD; Arya M Iranmanesh, MD; Bahar Mansoori, MD; Arash Bedayat, MD; Holman P McAdams, MD; Hamid Chalian, MD

Rapid and effective diagnosis of potentially life-threatening pericardial diseases remains a challenge due to their similarities of symptoms and signs, and complexity of their imaging findings.[1] Imaging has some clinical value, but it also has important limitations, underscoring the importance of familiarity for radiologists.[2] Understanding the management of pericardial abnormalities also helps radiologists to identify and convey important findings to referring clinicians.[3] This article reviews common acquired pericardial diseases, with a particular focus on clinical and hemodynamic significance, imaging findings, and management of more commonly encountered pathologies.

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Simple Pericardial Effusion

The pericardial space normally contains 15 to 50 mL of serous fluid acting as a lubricant between the visceral and parietal layers of the pericardium.[4] Pericardial effusion results from a pathologic accumulation of fluid, which expands this potential space.[5] Although most cases remain idiopathic, common causes are uremia, infections, connective tissue disorders like systemic lupus erythematosus (SLE), acute myocardial infarction, and cardiac intervention.[5-7]

Chest radiography gives limited clues to the cause of pericardial effusion, depicting only an enlarged cardiac silhouette that may represent cardiomegaly or pericardial effusion.[5] A large pericardial effusion can simulate a water bottle shape ("water bottle sign") on frontal radiography.[8] Furthermore, the "Oreo cookie sign" or "pericardial fat pad sign" (Figure 1) on lateral radiographs can indicate a pericardial effusion.[9]

Echocardiography represents a noninvasive, standard method for evaluating pericardial effusion.[5] However, in addition to its innate limitation in field of view, the acoustic window may be further reduced by severe pulmonary emphysema or obesity.[10] On echocardiography, pericardial fluid appears as a relatively echo-free space interposed between the epicardium and the pericardium.[11]

Computed tomography (CT) and magnetic resonance imaging (MRI) have several advantages over echocardiography, including anatomic assessment of a greater portion of the thorax with the potential to detect associated abnormalities.[5] Furthermore, CT and MRI are far less operator dependent.[5] MRI (as well as retrospective electrocardiography gated CT) may provide valuable information regarding cardiac function (Figure 1).[5] CT attenuation of pericardial effusion can vary based on the transudative or exudative composition of the effusion, with higher attenuation in exudative pericardial effusions. However, there can be considerable overlap between the attenuation of exudative and transudative effusions.

Pericardial effusion management focuses on treatment of underlying etiologies; however, pericardiocentesis and pericardiectomy may be indicated in symptomatic cases with rapid or large fluid accumulation.[5] Prognosis depends

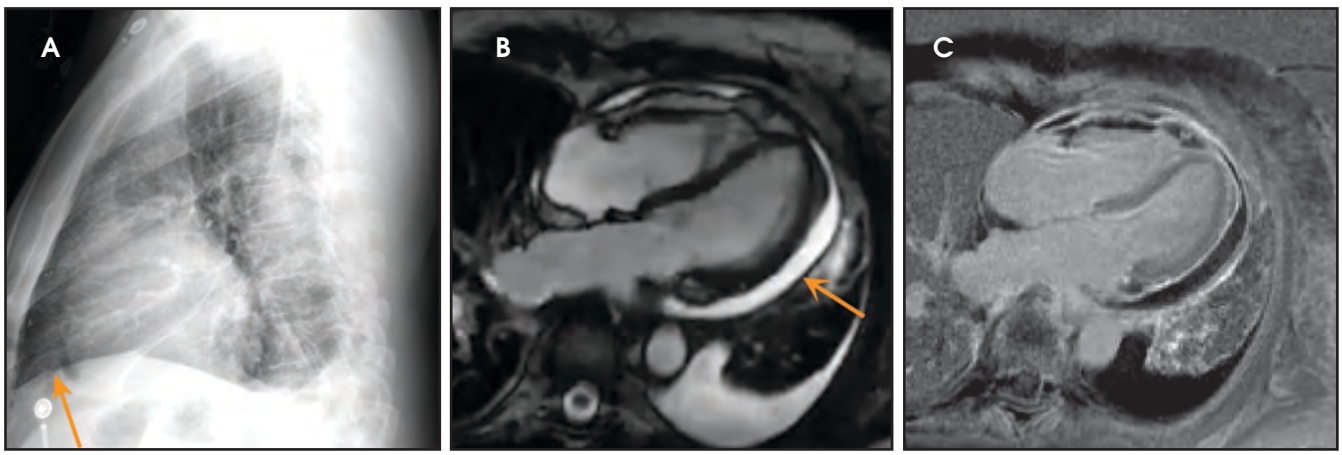

FIGURE 1. *Lateral (A) chest radiographic image shows the interface between low-density epicardial fat, the relatively higher-density pericardial effusion (arrow), and low-density pericardial fat ("Oreo cookie sign"). Four-chamber (B) cardiac MRI of a different patient shows intermediate signal epicardial fat sharply demarcated against the high-signal pericardial fluid (arrow). The inner visceral and outer parietal layers of the pericardium are appreciated as curvilinear low-intensity bands containing the high-signal fluid. Four-chamber (C) inversion recovery images null the fluid signal of the effusion, which now appears devoid of signal (black).*

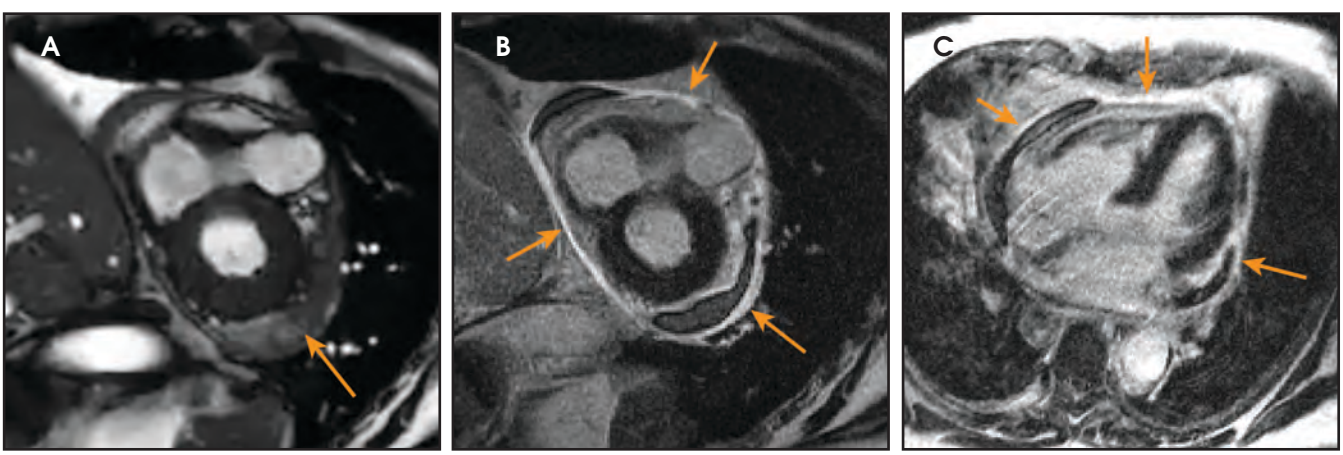

FIGURE 2. *Short axis (A) steady state free precession MRI of the heart shows a band of irregular, intermediate-signal tissue (arrow) encasing the heart and representing irregular thickening of the pericardium. Heterogeneous signal of the fluid located between the visceral and parietal layers of the pericardium is consistent with exudative effusion. Corresponding short axis (B) and four-chamber (C) delayed-enhancement MR image shows linear enhancement of the pericardium (arrows) confirming active pericardial inflammation/infection.*

on the underlying etiology; patients with neoplastic pericardial effusion generally have a poor prognosis, while those with idiopathic/viral pericarditis usually have a very good prognosis.[5]

Pericardial Tamponade

Pericardial tamponade is a life-threatening mechanical condition occurring when pericardial effusion increases pericardial pressure; thus, impairing diastolic filling of the heart.[12] This insufficiency leads to a decline in cardiac output and blood pressure.[13,14] Presentation may be either acute (with chest discomfort, dyspnea, and hypotension) or subacute (asymptomatic initially with gradual progression of symptoms).[12,13] A variety of pathologic conditions may result in pericardial tamponade, including infection, inflammatory processes, malignancy, and trauma.[12,14]

Echocardiography is considered a sensitive and rapid diagnostic tool.[15] An increase in the right ventricle (RV) dimension and a decrease in the left ventricle (LV) dimension on inspiration is suggestive of pericardial tamponade.[11,16] Diastolic collapse of the compliant RV signifies that pericardial pressure exceeds early diastolic RV pressure.[11,14] Detection of RA collapse is 100% sensitive, but less specific, for tamponade.[11,16] LV collapse is less common, owing to its wall thickness.[11,16] Typical findings of pericardial tamponade on CT and MRI include flattening or inversion of the right atrial or RV wall with compression of these chambers, inversion of the interventricular septum, distention of the superior and inferior vena cavae, and reflux of contrast into the azygos vein and inferior vena cava.[14] These findings are better appreciated on electrocardiographically gated cardiac studies.

The pericardial space in pericardial tamponade often requires urgent

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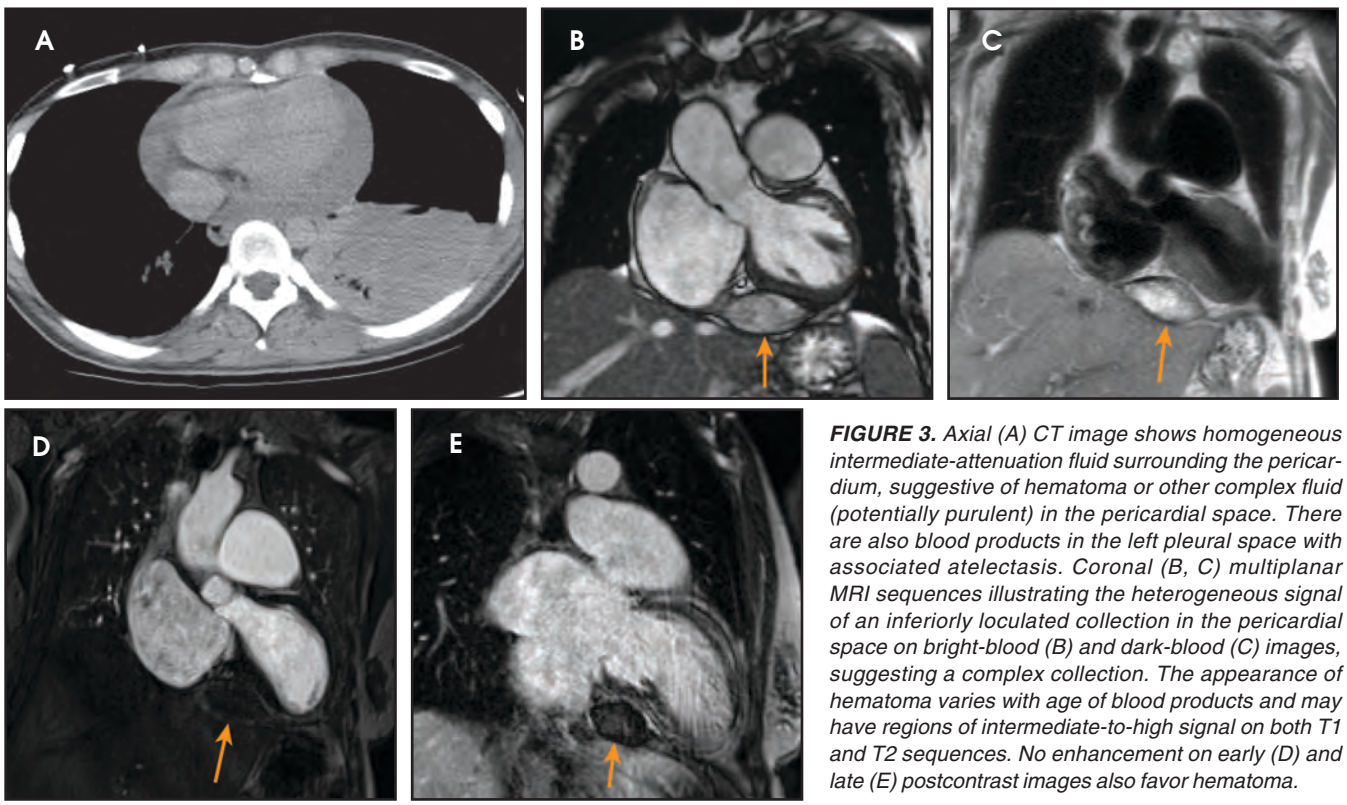

FIGURE 3. *Axial (A) CT image shows homogeneous intermediate-attenuation fluid surrounding the pericardium, suggestive of hematoma or other complex fluid (potentially purulent) in the pericardial space. There are also blood products in the left pleural space with associated atelectasis. Coronal (B, C) multiplanar MRI sequences illustrating the heterogeneous signal of an inferiorly loculated collection in the pericardial space on bright-blood (B) and dark-blood (C) images, suggesting a complex collection. The appearance of hematoma varies with age of blood products and may have regions of intermediate-to-high signal on both T1 and T2 sequences. No enhancement on early (D) and late (E) postcontrast images also favor hematoma.*

decompression.[13] Pericardiocentesis is performed in cases of acute cardiac decompensation;[17] the underlying cause should also be treated.[18] Pericardiocentesis may be performed by surgically placing a drain in the subxiphoid space.[13] Ultrasound-guided, percutaneous drainage with needle or catheter increases pericardiocentesis safety up to 20%.[13] Radiologists who perform thoracic procedures should be familiar with CT-guided pericardial drain placement and imaging findings suggestive of pericardial tamponade.[14]

Pericarditis

Pericarditis is an inflammation of the pericardium.[14] Its incidence is 0.1% in hospitalized patients and as high as 5% in emergency department patients with chest pain.[19] A variety of conditions may cause primary and secondary pericarditis.[14] Primary pericarditis presents as an isolated disorder of the pericardium, commonly with atypical chest pain (classically relieved by leaning forward) and variable constitutional symptoms.[20] Although pericarditis is most often idiopathic, several secondary etiologies have been identified, including iinfection, acute myocardial infarction, drug toxicity/reaction, radiation therapy, cardiac surgery, and systemic inflammatory conditions such as rheumatoid arthritis.[14,19,21] Patients presenting with acute pericarditis may describe recent symptoms suggestive of viral upper respiratory tract infection.[19]

Radiography in the setting of acute pericarditis is often devoid of specific findings.[19] Echocardiography, the modality of choice, demonstrates a characteristically thickened pericardium.[14] CT and MRI can improve visualization and further characterization, particularly following contrast administration.[14,22] Pericardial layers in acute cases show thickening and enhancement on CT, whereas irregularity or nodular thickening of the pericardium, with or without calcification, are highly suggestive of chronic pericarditis.[14,22] MRI may show similar findings on T1 postcontrast and bright-blood sequences.[14,23] T2 spin echo MRI demonstrates increased signal of the edematous pericardial tissues, attributable to increased fluid signal.[14,23] The addition of pulse sequences such as short tau inversion-recovery (STIR) further improves pericardium evaluation by nulling the signal from adjacent epicardial and pericardial fat, which also demonstrate high signal and may obscure the pericardium.[14,23] Contrast-enhanced MRI is helpful in evaluating pericardial inflammation by demonstrating linear enhancement of the pericardial layers resulting from active inflammation (Figure 2).[14,23]

Most cases of acute pericarditis remit spontaneously.[24] Treatment of noninfectious pericarditis largely involves systemic anti-inflammatory medications.[24] Non-steroidal anti-inflammatory drugs are considered the mainstay of treatment for uncomplicated presentations.[21] Glucocorticoids and colchicine may also be considered for those presenting with more severe and refractory cases.[24,25]

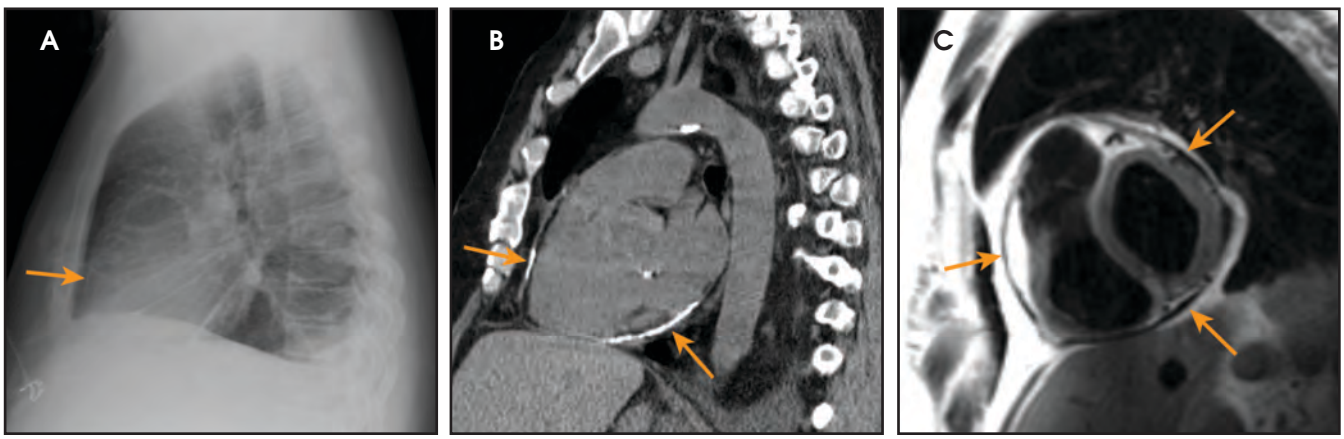

FIGURE 4. *Lateral (A) chest radiographic image shows subtle curvilinear increased density along the inferior aspect of the cardiac silhouette, suggesting pericardial calcification. Correlative sagittal (B) non-contrast CT image in the same patient confirms pericardial calcifications accounting for the radiographic findings. Short axis "dark blood" MR (C) demonstrates low signal, thickened pericardium correlating with pericardial calcification and fibrosis. Findings are suggestive of constrictive pericarditis.*

Pericardial Hematoma

Blood may accumulate between the visceral and parietal layers of the pericardium may occur following trauma; interventions include cardiac surgery and pericardiocentesis, due to neoplastic involvement and aortic dissection, with the latter having a dismal outcome.[23,26] Clinical presentation typically depends on the cardiac structure being compressed by the hematoma.[26] Although hemodynamic status may be preserved, acute pericardial hematoma may cause pericardial tamponade.[15]

Although echocardiography provides limited tissue characterization, the modality can provide functional cardiac assessment.[27,28] CT, showing blood product attenuation of the pericardial fluid, is sensitive but not specific (Figure 3).[4] MRI provides ideal tissue characterization (Figure 3); the signal of the hematoma depends on the age of collection: it is homogeneously high on T2 and intermediate on T1 sequences in the acute phase; heterogeneously high on T1 and T2 sequences in the subacute phase; and low on T1 and T2 sequences with a dark rim in the chronic phase.[23,29] No enhancement is expected on either CT or MR imaging.[4,23]

The management of pericardial hematoma involves either placing a percutaneous pericardial drain or emergent surgical drainage.[26]

Constrictive Pericarditis

Constrictive pericarditis should be considered when diastolic ventricular filling is impaired in the setting of thickened fibrotic pericardium.[30] Although the condition is most often idiopathic or viral, a suspected inciting factor such as radiotherapy, intervention, bacterial or tuberculous infection, and metabolic disturbance (uremia) may be identified.[31] Pericardial thickness greater than 4 mm is the hallmark of constrictive pericarditis. However, thicknesses less than 4 mm also can been seen in constrictive pericarditis.[14] The extent of thickness has no direct relationship with the level of hemodynamic compromise.[4] Constrictive pericarditis presents as potentially reversible heart failure with symptoms and signs including fatigue, orthopnea, and tachycardia.[23,32] Differentiating constrictive pericarditis from restrictive cardiac pathologies is often challenging, owing to similarities in clinical presentation and echocardiography findings. Cardiac MRI can help to exclude restrictive cardiomyopathy diseases.[4]

Although constrictive pericarditis is not directly visible on radiography, several indirect findings, such as pulmonary edema and pericardial calcifications, are suggestive (Figure 4).[14] Echocardiography often serves as the first dedicated cardiac imaging modality.[32] The pericardium typically appears abnormally thickened, potentially with regions of artifact due to calcification.[32] Doppler echocardiography demonstrates signs of restrictive pathology such as impaired diastolic filling without augmentation of central venous return on inspiration.[32,33] "Septal bounce," a paradoxical bouncing motion of the interventricular septum on echocardiography or MRI is a hallmark of constrictive pericarditis and is highly specific and relatively sensitive.[34] The thickened fibrotic and/or calcified pericardium has low signal intensity on T1 and T2 spin-echo MR images and at steady-state free precession imaging (Figure 4).[14,23] CT is very sensitive to minimal amounts of pericardial calcification and thickness severity before surgery (Figure 4).[14] Moreover, other abnormalities resulting from increased cardiac filling pressures, such as atrial enlargement, dilatation of caval and hepatic veins, pleural effusion, and ascites may be easily recognized on CT.[4,14] Whereas pericardial enhancement suggests inflammation, no enhancement may appear in end-stage chronic pericardial fibrosing.[14]

Some cases with transient constrictive pericarditis may respond to medical therapy, but severely affected patients may be candidates for partial or total pericardiectomy.[4,31]

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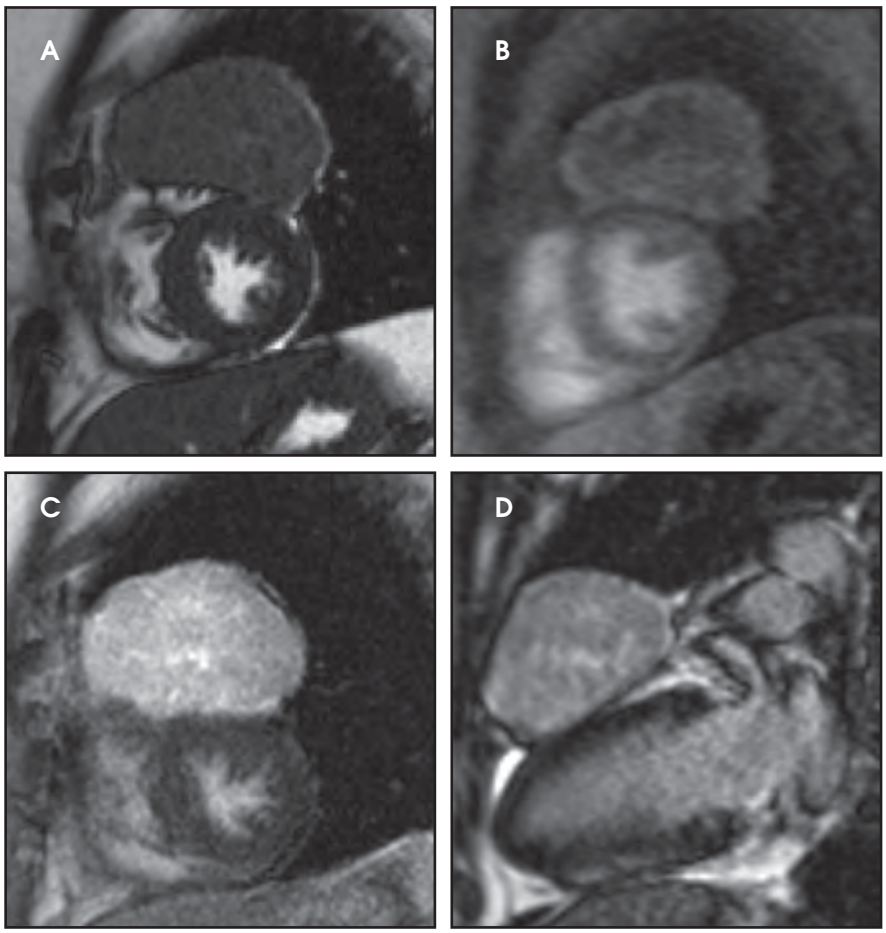

FIGURE 5. *Short-axis (A), bright-blood MRI sequences show a large mass superior to the heart, inseparable from the pericardium, with heterogeneous signal similar in intensity to the soft tissues of nearby viscera. Short-axis (B), early phase postcontrast image shows enhancement of the mass. Short-axis (C) and two-chamber (D), postcontrast delayed-enhancement images demonstrate heterogeneous enhancement of the mass characteristic of neoplasm. This was a proven solitary fibrous tumor.*

Effusive Constrictive Pericarditis

Effusive constrictive pericarditis is a rare inflammatory syndrome in which constrictive pathology (specifically involving the visceral layer) and compressive pericardial effusion exist simultaneously.[23] The diagnosis should be considered when intracardiac pressures remain elevated following pericardiocentesis.[35] The effusive constrictive pericarditis has been reported in 1.2% of patients with effusive pericarditis, and 6.8% of patients who underwent pericardiocentesis.[36] The mortality rate is high (~ 60%).[36] Potential etiologies and manifestations of effusive constrictive pericarditis overlap with constrictive pericarditis.[23,35] Underlying etiology has an important impact on patient outcomes.[36]

Optimal diagnosis requires measuring both intra-pericardial and right atrial/biventricular pressures before and after pericardiocentesis.[35] Noninvasive approaches such as echocardiography, CT, and MR imaging may be useful in demonstrating thickened pericardium in constrictive pericarditis but not in effusive constrictive pericarditis.[37] Doppler echocardiography and MRI can assess cardiac hemodynamics and confirm pericardial inflammatory changes, respectively.[35,38]

Although many patients will require visceral pericardiectomy, some patients may improve spontaneously or respond to more conservative medical therapy with anti-inflammatory agents and treatment of underlying conditions.[23,35]

Pericardial Tumor Invasion

Metastatic pericardial diseases are more common than primary pericardial tumors.[4] Approximately 10% of patients with malignancy have pericardial invasion at autopsy.[4] Malignant cells from other organs may metastasize to the pericardium by lymphatic or hematogenous routes, in addition to direct, local extension.[4] Common pericardial metastases include lung and breast cancers, melanoma, leukemia, and lymphoma.[4,39] Primary pericardial tumors such as solitary fibrous tumor are less likely (Figure 5). Cardiac function is impaired in up to 30% of patients, owing to arrhythmias and compromised ventricular contraction.[39] Clinical presentation is nonspecific and depends on the size and location of the lesions.[39]

Echocardiography may be limited by reduced tissue characterization.[40] MRI and CT offer a greater field of view to evaluate the extent, and potentially the origin, of metastases.[40,41] CT findings include enhancing pericardial nodules or masses.[4,42] MRI has higher tissue characterization compared to echocardiography and CT, allowing better assessment of cardiac and extracardiac tumor extension.[40,43] Most pericardial tumors enhance with contrast and demonstrate low signal intensity on T1 images and increased signal on T2 images (Figure 5).[41] Positron emission tomography (PET) in combination with CT has also demonstrated particular utility in staging and follow-up of pericardial tumors.[41,44]

Neoplastic involvement of the pericardium may remain unknown until autopsy.[41] The prognosis of pericardial tumor invasion is poor.[43] Death from pericardial invasion usually occurs as the result of tamponade.[4]

Conclusion

Understanding the diagnostic imaging features, clinical significance, and management of acquired pericardial abnormalities will help radiologists improve

their identification of these diseases and improve their communication with referring clinicians.

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The New IR Residency Is Here: Is Your Practice Ready?

Nicole Keefe, MD; Jamie Doster, MD

Interventional radiology (IR) has evolved over the past several decades as interventional radiologists continue to become more clinically minded. Newer trainees are being instilled with the mindset that IR physicians are no longer "hired guns" who perform procedures on demand, but instead are specialists in their own right who determine procedural validity, discuss therapeutic options, including medical and surgical management, and follow patients post-procedure.

This perspective reflects a significant change from the times of Charles Dotter and one that is increasingly being adopted by many institutions. Indeed, the next generation of interventional radiologists seeks to take ownership of their patients' care.[1] Over time, this mindset is expected to grow both IR and diagnostic radiology (DR) practices through increased referrals, higher-level cases, and greater volume of diagnostic imaging related to pre- and post-procedure management.

IR Training: New and Improved

The original pathway to more clinically oriented IR physicians was established in 2000 through the Diagnostic and IR Enhanced Clinical Training (DIRECT) program in 2005. The Society of Interventional Radiology (SIR) has since worked tirelessly to implement a paradigm designed to train a new generation of interventional specialists.[2] The IR Integrated Residency (IRIR), approved in 2014, graduated its first small group of internally transferred residents in 2018 and will graduate its first fully matched class in 2021. As of October 2020, 89 institutions offer the IRIR, demonstrating the universal acceptance this pathway has received for training IR physicians.[3]

The IRIR allows medical students to match directly into IR. After completing a one-year internship, residents move on to a five-year program consisting of three years of core DR training and two years of IR clinical training. Residents who do not participate in the IRIR can transfer into IR from DR through one of two paths: the Early Specialization in IR (ESIR) route, followed by an IRIR residency; or a traditional DR residency followed by an independent IR residency. This option may take up to seven years, as compared to six years in the IRIR (Figure 1).[3,4]

Most current and recent IR residents and fellows believe the IRIR will improve training, a belief supported by the growing number of applicants---more than 400 for the 2019 match cycle.[5,6] Nearly half of trainees surveyed by Hoffmann, et al, agreed that the traditional one-year fellowship is insufficient to prepare IR physicians for practice. Only 20 percent agreed that an IR residency would not provide adequate DR training for their future job.

The IRIR increases the amount of time trainees spend performing procedures, seeing patients in the IR clinic, rotating with consulting services, and managing critically ill patients in the intensive care unit (ICU) while also receiving DR training.[7] The average trainee rotates through 3.5 non-IR clinical specialties during the postgraduate years 2 through 6, although variability exists among programs.[5] Rotations through vascular surgery, ICU, oncology, and hepatobiliary surgery, for example, can increase a trainee's comfort with caring for and performing procedures on these populations.

The increased IR training also provides further experience in the complex array of procedures performed by interventional radiologists. More time in IR and other services comes at the cost of less time in DR rotations; however, this decrease is not significantly different from other programs that offer global health or research tracks, or mini-fellowships followed by year-long fellowships, as those trainees also spend less time in DR.

Private practices will need to adapt to the more clinically oriented paradigm, paralleling other specialties such as vascular surgery and interventional cardiology. Providing sufficient clinical time to care for and treat complex IR patients is crucial to a thriving IR practice. In the near term, this may seem a detriment, as the approach initially may not generate relative value units (RVUs). On a larger scale, however, it offers an opportunity to solidify private practice contracts with hospitals. Many purely diagnostic

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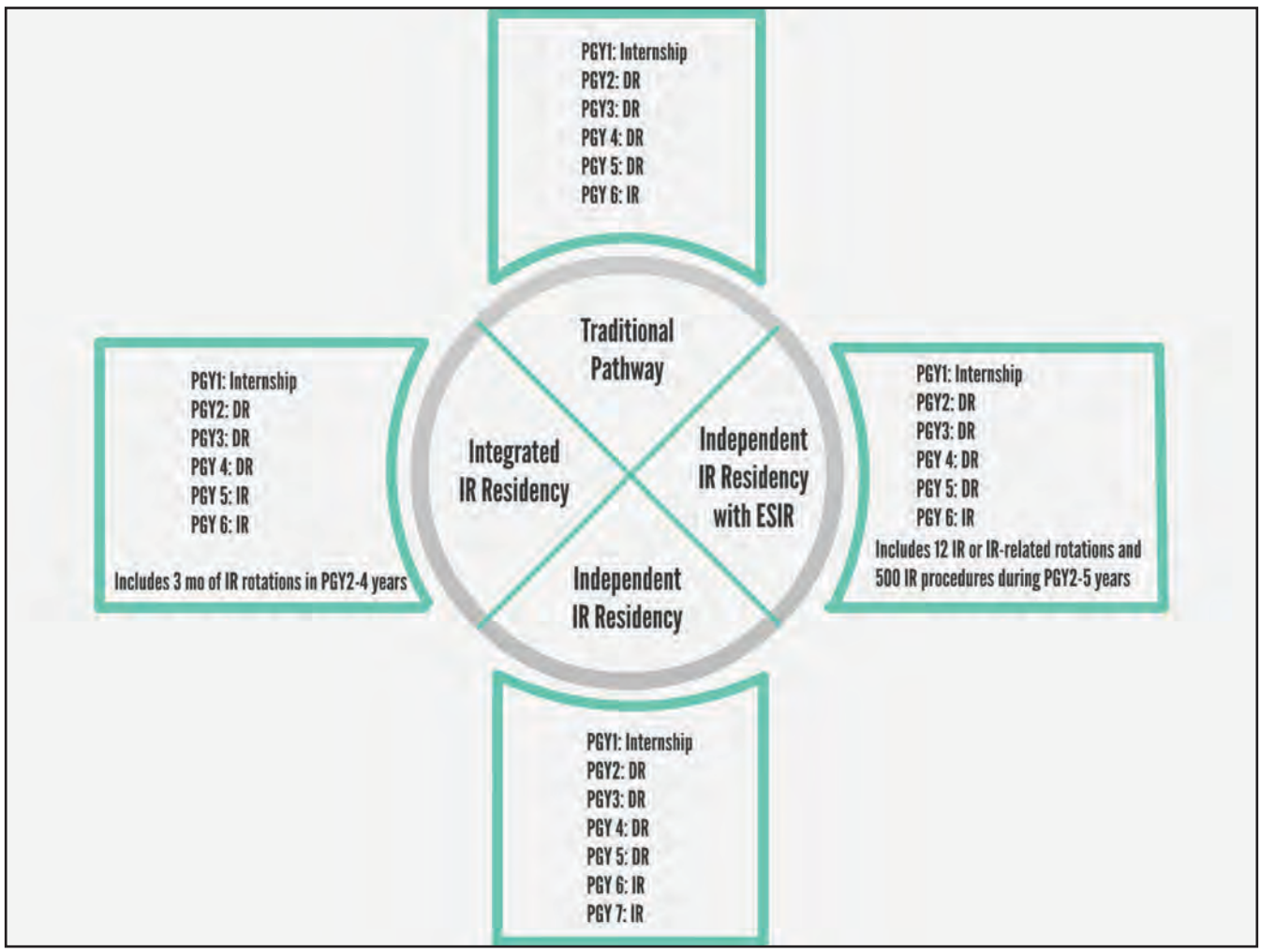

FIGURE 1. *Traditional and New Training Models for Interventional Radiology.*

imaging services can be performed remotely or via teleradiology, but an IR component may secure the local presence of a DR practice, as well.

Additionally, as IRs develop and build their own practices, they can generate imaging and evaluation and management (E&M) revenues. Many DR practices are being bought by larger corporations, and contracts are being sold to teleradiology, but the same cannot be said of IR practices that require boots on the ground. Maintaining an active practice that evolves with the growing clinical nature of IR will solidify a DR/IR or solo IR private practice presence in a hospital system or outpatient setting.

Private Practice Group Concerns

Hiring competitive and talented IR physicians is a must for IR section heads in an expanding physician-owned IR/DR private practice. In previous years, private practice groups knew what to expect from graduates of programs with a known training paradigm. However, since IR residency programs are producing a novel type of IR graduate, new questions are arising for private practices: Are these IR graduates ready to handle the heavier workload that goes along with many private practices? Can they provide work of similar quality from a diagnostic standpoint, even if DR is not a large percentage of their daily workload? It seems reasonable to be concerned that new IR residents may lack DR quality and efficiency.

Key to answering these questions is looking at how a program has evolved to handle the new educational needs of IR residents. Evaluating how a program has transitioned to the IR residency is important; it must continue to value the need for, and provide, high-quality diagnostic training. It must continue to mandate adequate time on valuable, high-yield diagnostic rotations while also allowing trainees to focus on their IR training. This can be vital to success in the private practice world. Unfortunately, ascertaining this information from an IR candidate can be difficult for a private practice; the onus ultimately lies on the training program to produce skilled and versatile IR residents.

Forthrightness is also important on the part of private practice groups to convey the potential diagnostic demands of group members. Informing interviewing candidates of expected diagnostic contributions enables them to decide if those expectations align

with their career goals and may help to ensure their long-term job satisfaction. Many new IR trainees may be seeking a career without DR imaging responsibilities; the practice models now available--- mixed private practices in academic, as well as solo IR practices---may afford these opportunities.

A final consideration for a private practice is whether it is truly ready to hire the new generation of IRs. These physicians are trained to work in environments where they are viewed as clinical specialists intimately involved in patient care. Cultivating this culture takes time and effort, which are not easily translated into traditional radiology RVU-type metrics. Providing space for the IR section to function as a highly valued clinical entity within the group is key to success.

Current IR practice not only includes reimbursement through procedural CPT codes but also through E&M codes. However, this also requires dedicated infrastructure, time, and personnel; practices that include IR must accommodate these requirements.[1] This may be challenging for small private practice groups or those that are not highly specialized. However, the trend in private practice is toward sub-specialization and growth, which hopefully will allow today's new IR specialists to function more effectively in these settings.

Recent IR Residency Graduate Concerns

New IR residents have many questions when exploring private practice opportunities: IR-only or joint IR/DR practice? Will I be permitted the time necessary to maintain the clinical nature of IR? Am I prepared to read diagnostic studies?

The answers to these questions are complicated by each practice's unique structure, often relating to DR and call responsibilities. The graduate's decision frequently depends on the actual or perceived DR support of IR and the time required in DR. Although DRs typically generate more RVUs, support for the clinical nature of IR is crucial for a high-functioning IR practice capable of performing more than routine biopsies and drain placements.

Building an IR practice by speaking with referring providers and hosting community educational sessions is a slow process, but it is one that will ultimately yield dividends as an RVU generator for DR and IR alike. The amount of time required on DR will be vary with practice, and newly minted IR physicians will have to decide how much time they are willing to dedicate to DR. In a joint practice, dedicated DR days helps to foster a symbiotic relationship between colleagues. They also maintain diagnostic skills in the event of changes in career or personal circumstances.

Preserving the clinical nature of IR in private practice is a challenging task that also requires educating the billing department. Proper coding and billing of non-procedural components, including inpatient and outpatient E&M billing, will help secure appropriate reimbursement. Regular consultation with the financial administration is crucial. In addition, communication with DR colleagues is vital to maintaining relationships within the group. Documenting cases and consultations permit DR colleagues to appreciate the required to care for each patient. When possible, assisting with image interpretation between IR cases fosters goodwill and a team-player reputation.

Maintaining diagnostic skills throughout the IR residency is not as difficult as it may seem. Interventional radiologists routinely read their own pre- and post-procedural imaging and practice their skills in vascular imaging and body MRI, especially with respect to oncology patients. Many programs may also provide diagnostic rotations during the PGY5 and PGY6 years in order to keep up to date on DR skills.

Neuroradiology, musculoskeletal radiology, nuclear medicine, pediatric radiology, and mammography may prove more challenging in this respect, but quality improvement conferences are a great option to catch blind spots. Most new practices will conduct short-term reviews of diagnostic studies to appropriate reading pace and level, serving as an added level of protection for a newly practicing physician.

Conclusion

Incorporating new IRIR graduates is a significant change for most private practices. But sufficient communication and support will help ensure that these physicians can continue to practice clinical IR while contributing RVUs to the practice. Graduates will require patience and perseverance to build a practice that best suits their needs and the needs of their patients, and they must also be sure to maintain the diagnostic skills necessary to meet the demands of the private practice.

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Imaging Findings in the Setting of Rhabdomyolysis

Emily Neal; Steve Burky, MD

Rhabdomyolysis is a syndrome characterized by the disruption of skeletal muscle leading to the release of intracellular muscle constituents, including myoglobin and creatine kinase, into the circulation and extracellular spaces. The clinical presentation is broad, ranging from asymptomatic to life-threatening.

The most significant complication is acute kidney injury, which occurs in up to 40% of patients. Other serious complications include disseminated intravascular coagulation and compartment syndrome.[1] Risk factors that predict a poor outcome (eg, a need for renal replacement therapy, or death) include advanced age, female sex, initial creatine, creatinine phosphokinase, phosphate, calcium, and bicarbonate levels.[2] Characteristic symptoms of rhabdomyolysis include muscle pain, weakness, and dark urine, although over half of patients do not report muscle symptoms.[3] Physical findings include muscle tenderness and weakness. Muscle swelling typically occurs later in the hospital course during fluid repletion.

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Creatine kinase, the most sensitive lab abnormality for muscle injury, is released into the bloodstream within 12 hours of injury. Although no specific threshold has been established for the diagnosis of rhabdomyolysis, a creatine kinase level of at least five times the upper limit of normal (ie, 1000 IU/L) is commonly used. A creatine kinase level of >5000 IU/L generally indicates a degree of muscle injury sufficient to cause acute kidney damage. Myoglobinuria is responsible for the brown to red urine of patients with this condition.

Additionally, the accumulation of myoglobin, a nephrotoxin, is responsible for the acute kidney injury of rhabdomyolysis. However, myoglobin has a short half-life and therefore may not be detected in the serum or urine of patients experiencing significant rhabdomyolysis.[4,5]

Imaging Considerations

Rhabdomyolysis is not diagnosed specifically with imaging, but rather through a final pathway shared by numerous etiologies resulting in muscle damage. Imaging findings depend on the underlying cause, although typically the muscles will display signs of edema and/or hemorrhage.

On computed tomography (CT), edematous muscles are typically hypodense and may be enlarged (Figure 1A). As muscle damage progresses, peripheral enhancement surrounding areas of infarcted or necrotic tissue may be demonstrated on postcontrast images (Figure 1B).

Magnetic resonance imaging (MRI) is more sensitive than CT to muscle damage.[6] Involved muscle is usually isointense on T1 sequences, although mild T1 hyperintensity owing to hemorrhage or protein concentration may be demonstrated, particularly on fat-saturated sequences (Figure 2). The affected musculature typically displays high signal on T2 or short tau inversion recovery (STIR) images (Figure 2).[7] The broad differential diagnosis of muscle edema can be narrowed by separating

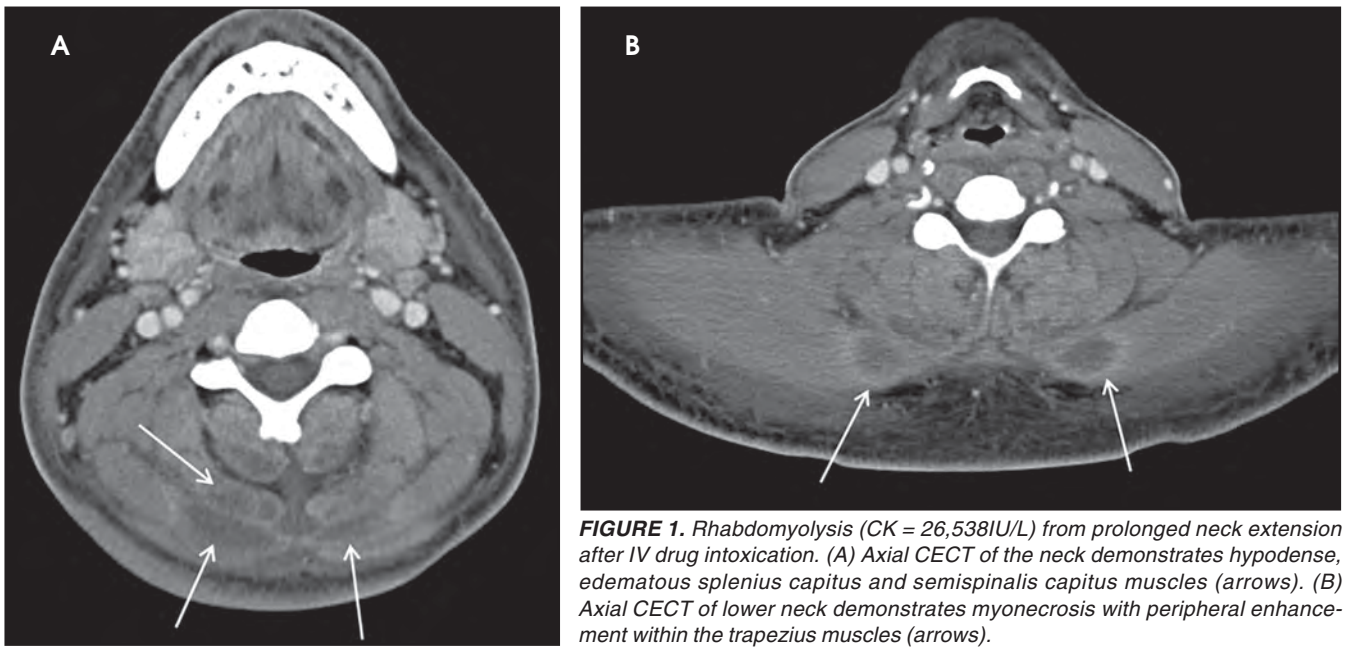

FIGURE 1. *Rhabdomyolysis (CK = 26,538IU/L) from prolonged neck extension after IV drug intoxication. (A) Axial CECT of the neck demonstrates hypodense, edematous splenius capitus and semispinalis capitus muscles (arrows). (B) Axial CECT of lower neck demonstrates myonecrosis with peripheral enhancement within the trapezius muscles (arrows).*

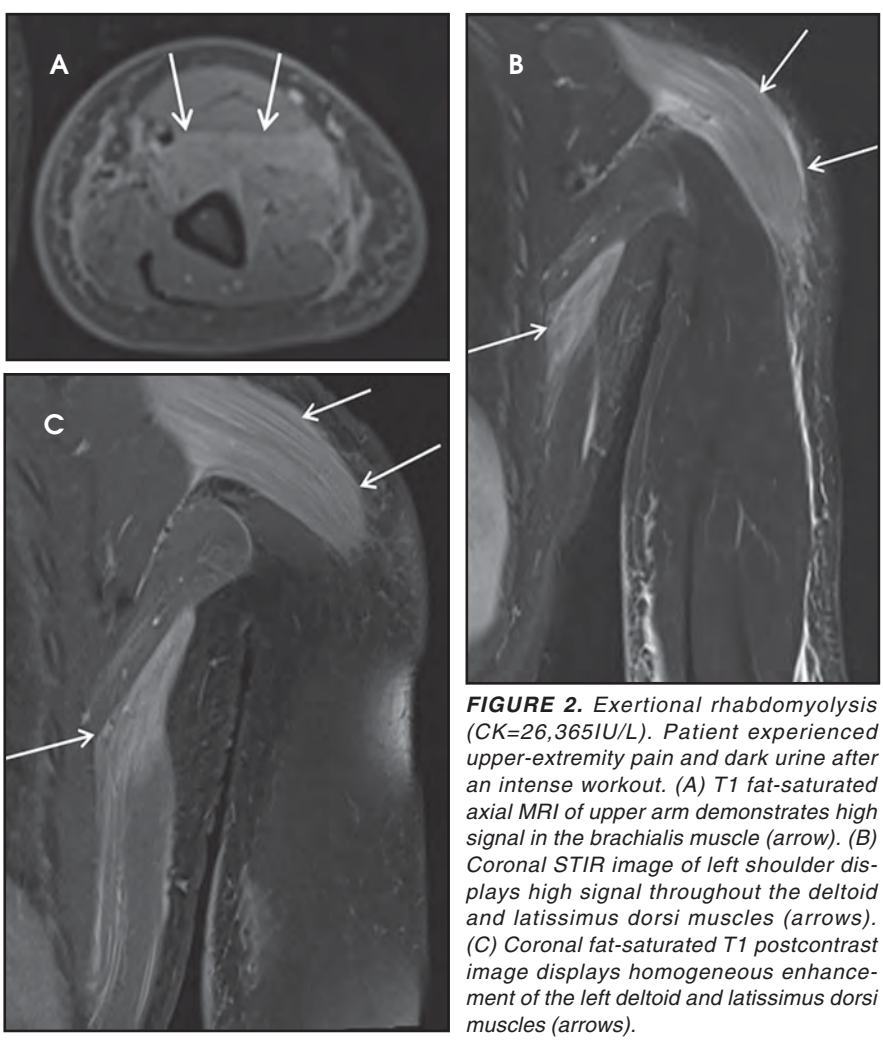

FIGURE 2. *Exertional rhabdomyolysis (CK=26,365IU/L). Patient experienced upper-extremity pain and dark urine after an intense workout. (A) T1 fat-saturated axial MRI of upper arm demonstrates high signal in the brachialis muscle (arrow). (B) Coronal STIR image of left shoulder displays high signal throughout the deltoid and latissimus dorsi muscles (arrows). (C) Coronal fat-saturated T1 postcontrast image displays homogeneous enhancement of the left deltoid and latissimus dorsi muscles (arrows).*

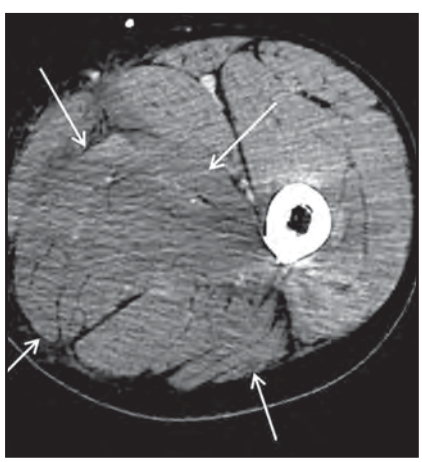

FIGURE 3. *Rhabdomyolysis (CK= 310,541 IU/L) and compartment syndrome due to prolonged immobilization while intoxicated. CECT of the left thigh demonstrates decreased enhancement of multiple muscles, including the adductor longus, adductor magnus, biceps femoris, and semitendinosus (arrows). The patient underwent emergency fasciotomy and debridement.*

cases into symmetric or asymmetric patterns.

Symmetric causes of muscle edema are typically secondary to inflammatory (polymyositis, dermatomyositis, human immunodeficiency viral associated (HIV), myositis) and drug-related myopathies. Asymmetric edema is more likely to be caused by trauma,

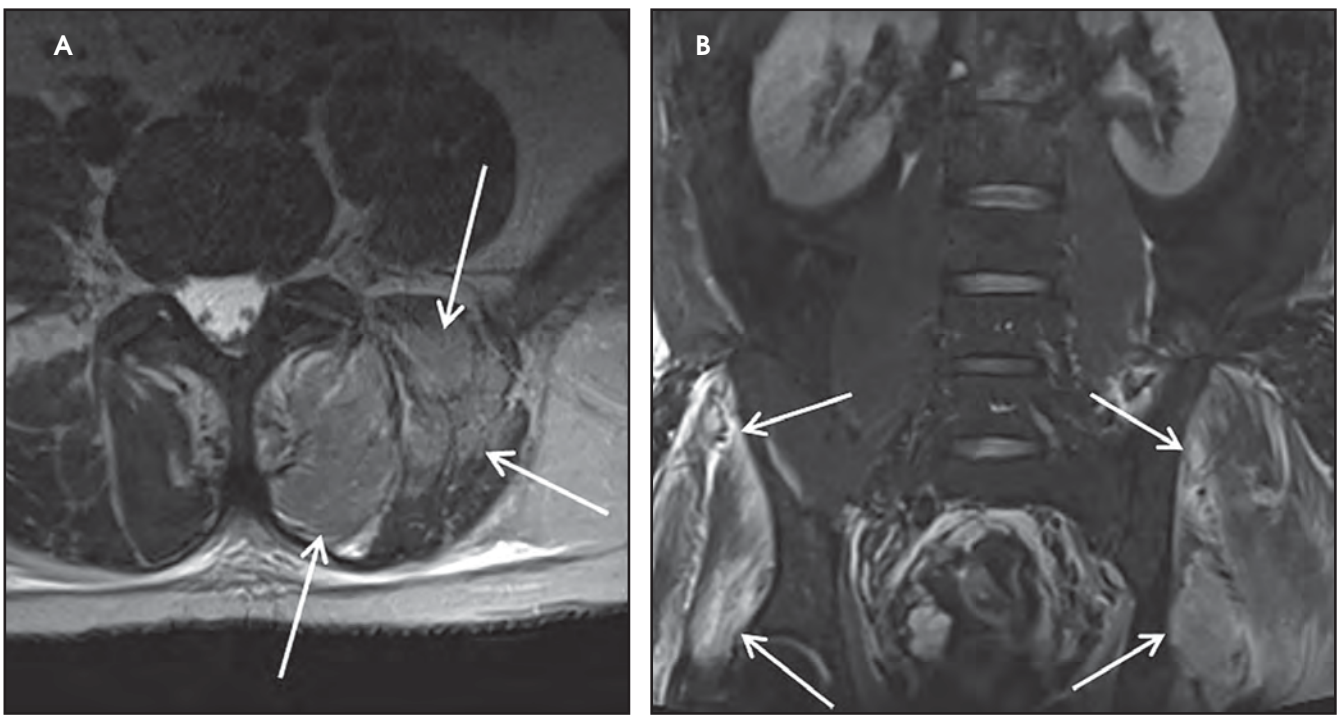

FIGURE 4. *Patient found unconscious after fentanyl overdose (CK 155,355). (A) Axial T2 MRI of the lumbar spine demonstrates high signal edema in the left paraspinal musculature (arrows). (B) Coronal STIR MRI of the pelvis displays high signal throughout the gluteal muscles (arrows).*

pyomyositis, radiation, myonecrosis, denervation, and compartment syndrome.[8] Following gadolinium-based contrast administration, involved muscles may demonstrate homogeneous enhancement prior to liquefaction or heterogeneous enhancement (stipple sign), reflecting viable tissue intermixed with necrotic muscle (Figure 2).[8] Scintigraphy is not a primary imaging modality in the setting of rhabdomyolysis, although muscle injury may be demonstrated on bone scans.

Acute compartment syndrome resulting from elevated compartmental pressure is a complication of rhabdomyolysis. The diagnosis is clinical and supported by an abnormal intracompartmental pressure measurement. Imaging plays a limited role in diagnosing acute compartment syndrome, but it may demonstrate normal or increased T1 signal within muscle, owing to hemorrhage and increased T2 signal secondary to edema. Decreased enhancement on CT or MRI within the compartment can be demonstrated on postcontrast images (Figure 3).[8]

Causes of Rhabdomyolysis

Any condition that leads to extensive muscle damage may theoretically result in rhabdomyolysis. A study of 425 adult patients with rhabdomyolysis found drug or alcohol abuse, medicinal drug use, and immobility to be leading causes.[9] The multitude of etiologies can be organized into three main categories:

- Trauma or long-standing compression of muscle (prolonged immobilization, crush injury, electric shock, muscle tear);
- Nontraumatic (strenuous exercise, seizures, delirium tremens, muscular dystrophy, hyperthermia, heat stroke, diabetic ketoacidosis, myopathy); and,
- Muscle toxins (illicit drugs; prescription drugs, including statins; influenza, HIV, and herpes virus; bacterial infection; snake venom).[1,5]

Muscle Compression or Trauma

Muscle compression during prolonged unconsciousness, rehabilitation, or surgery may lead to muscle oxygen deprivation, eventually resulting in muscle necrosis and rhabdomyolysis. Muscle compression resulting in ischemia can develop after drug or alcohol intoxication in which the patient has been lying or sitting in one position for a prolonged period of time (Figures 4,5). Crush injuries and blunt trauma are also common etiologies of rhabdomyolysis, particularly in the elderly. Amongst 167 patients with rhabdomyolysis, all of whom were over 65 years, 56.9% of cases were caused by falls.[10] In the setting of a crush syndrome, such as from a building collapse or automobile crash, rhabdomyolysis occurs once the muscle compression is relieved. Injuries related to high-voltage electricity (electrocution, lightning strikes) cause rhabdomyolysis in up to 10% of survivors.[1]

Nontraumatic Muscle Damage

Rhabdomyolysis may occur when the metabolic demands of normal muscle exceed the energy supply. Although serum creatine kinase naturally rises after strenuous exercise, rhabdomyolysis typically occurs when exertion generates

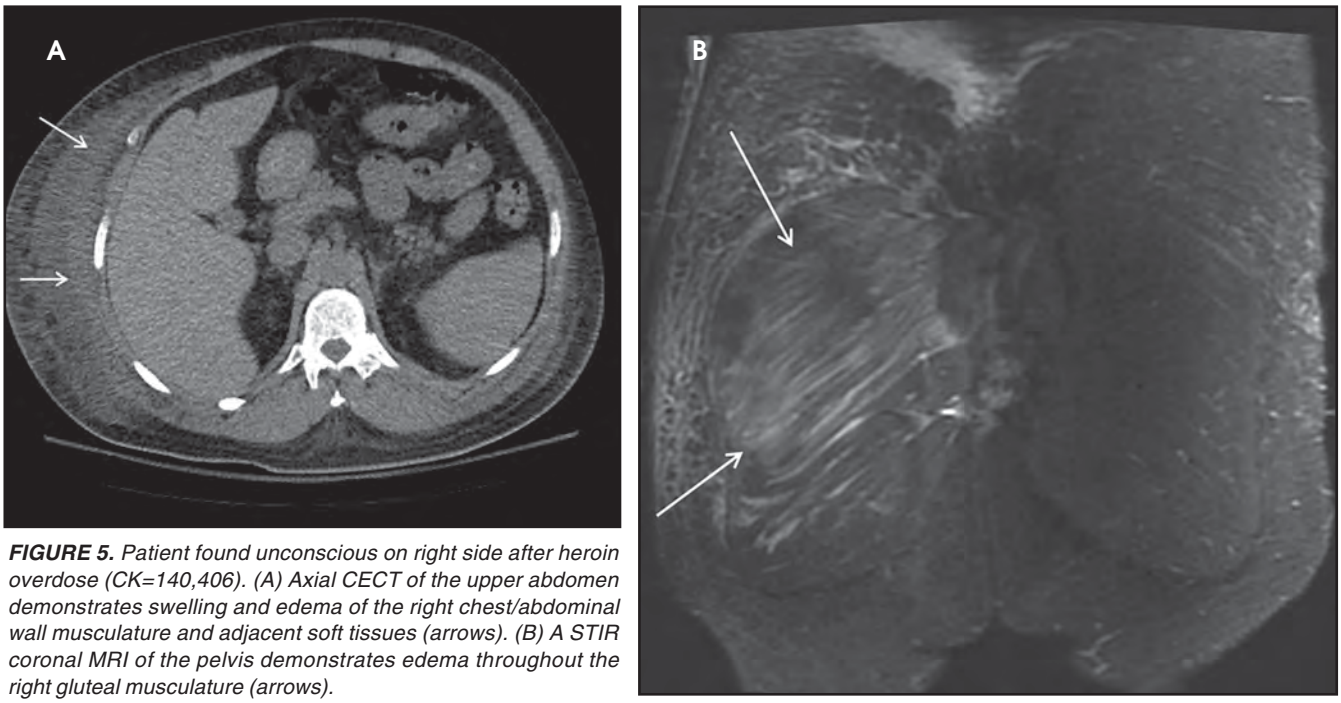

FIGURE 5. *Patient found unconscious on right side after heroin overdose (CK=140,406). (A) Axial CECT of the upper abdomen demonstrates swelling and edema of the right chest/abdominal wall musculature and adjacent soft tissues (arrows). (B) A STIR coronal MRI of the pelvis demonstrates edema throughout the right gluteal musculature (arrows).*

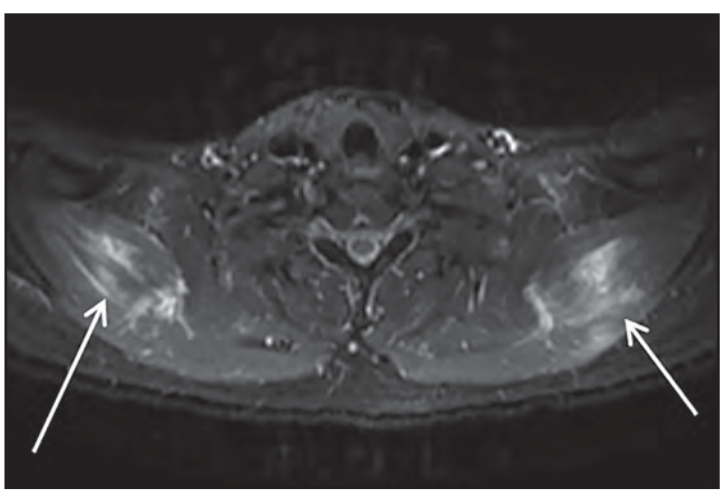

FIGURE 6. *Patient presented with arm weakness and paresthesias after prolonged, overhead, military-style training (CK=13,645). Axial fat-saturated T2 MRI of the shoulders demonstrates high-signal edema within the deltoid muscles (arrows).*

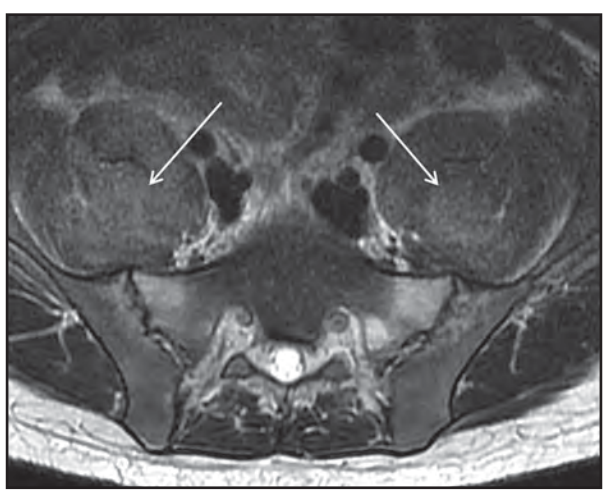

FIGURE 7*. Patient with back pain and rhabdomyolysis following a prolonged seizure (CK=23,002). Axial T2 image of the pelvis demonstrates high-signal edema with the psoas muscles (arrows).*

levels of pain and fatigue beyond that which would normally compel an individual to stop exercising. Factors such as competitive athletic or military training, extreme sports, and peer pressure during group exercise may predispose individuals to this level of exertion (Figures 2,6). Compounding risk factors include insufficient physical training and exertion in hot and humid conditions. Additionally, pathologic muscle exertion during delirium tremens, psychotic agitation, and seizures (Figure 7) may result in rhabdomyolysis.[3] Other causes of nontraumatic muscle damage include malignant hyperthermia, neuroleptic malignant syndrome, and heat stroke.[1,3]

Muscle Toxins

Prescription medications and abused substances may produce a myopathy leading to rhabdomyolysis. Statin medications are a well-known cause of muscle toxicity and rhabdomyolysis (Figure 8), especially in patients with predisposing conditions such as hypothyroidism, those on high doses of these medications, advanced age, and female sex.[1,12,13] Other classes of drugs that can cause rhabdomyolysis include psychiatric agents, non-statin lipid-lowering agents, and antihistamines.

FIGURE 8. *Patient with neck and extremity pain, amber-colored urine, and rhabdomyolysis. Known risk factors included a statin (atorvastatin calcium) as well as alcohol use. Sagittal T2 image of the right side of the neck demonstrate edema in the longus colli musculature (arrows).*

Substance abuse can result in metabolic acidosis and induce rhabdomyolysis. Alcohol, cocaine, heroin, and amphetamines have all been implicated. Myopathy secondary to systemic drug use typically affects the buttocks, quadriceps, adductors, and calf muscles in a symmetric distribution.[8] Toxins, including poisons and venoms, may directly interfere with muscle energy production, cause electrolyte abnormalities, or degrade the muscle cell.[14,15]

A vast number of bacterial and viral infections (eg, influenza, HIV, herpes simplex) can cause muscle damage. Infections that invade the muscle cells may lead to muscle necrosis. Some infections may generate toxins that inhibit metabolic activity, inducing rhabdomyolysis.[1] MRI of pyomyositis-induced rhabdomyolysis demonstrates swelling of involved muscles on T1 images. T2 images display increased muscle signal owing to pus and edema (Figure 9). Following contrast administration, small fluid collections representing myonecrosis or larger, non-enhancing abscesses may be demonstrated.[8]

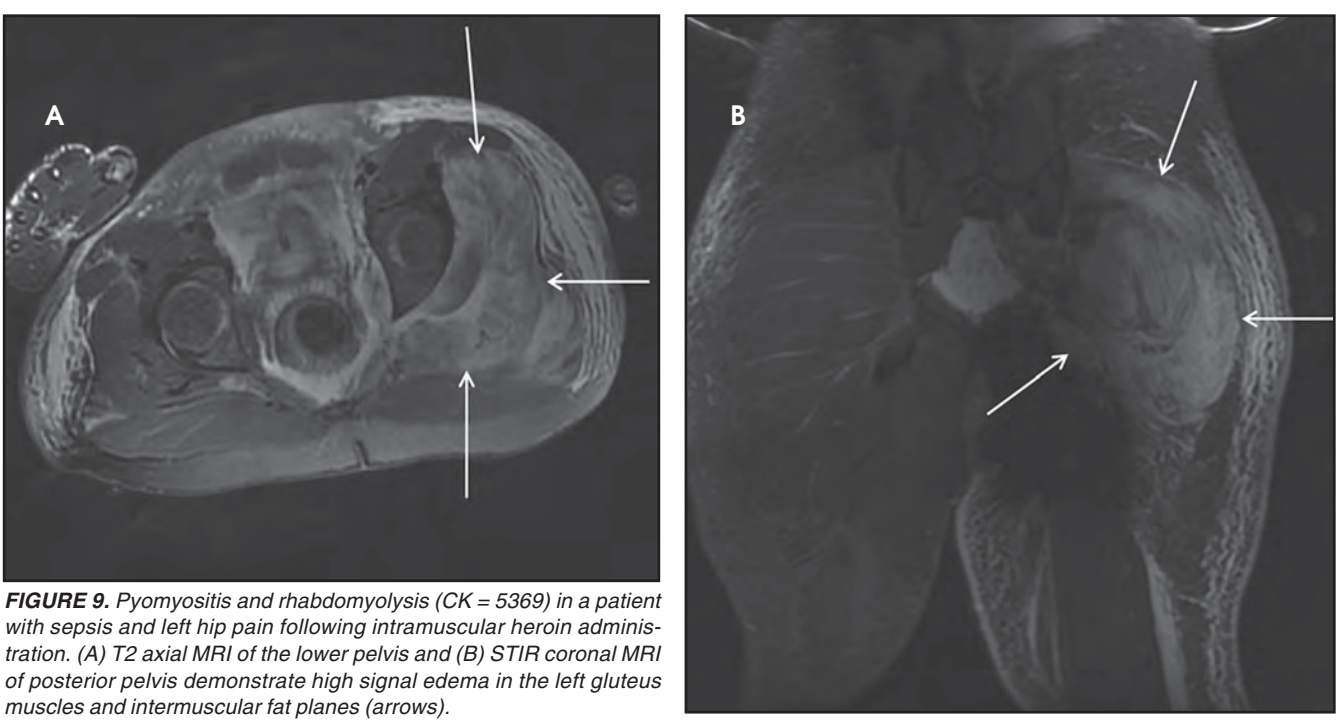

FIGURE 9. *Pyomyositis and rhabdomyolysis (CK = 5369) in a patient with sepsis and left hip pain following intramuscular heroin administration. (A) T2 axial MRI of the lower pelvis and (B) STIR coronal MRI of posterior pelvis demonstrate high signal edema in the left gluteus muscles and intermuscular fat planes (arrows).*

Rhabdomyolysis Treatment

The specific cause of muscle damage, such as drugs, toxins, or infection, should be identified and, where possible, eliminated.[15] Intravenous fluid replacement to achieve a urine output of 300 mL/h is important to prevent acute kidney injury. Similarly, bicarbonate administration can prevent acute kidney injury by increasing urine pH, which helps mitigate myoglobin toxicity.[15,16] Closely monitoring patients for fluid and electrolyte abnormalities is essential for preventing metabolic disturbances. Patients with severe kidney damage may require dialysis;[17] those with suspected acute compartment syndrome require urgent surgical consultation.

Conclusion

Rhabdomyolysis is a complex syndrome characterized by significant muscle damage and subsequent release of muscle components into the bloodstream and extracellular spaces. The most significant complication is acute kidney injury. The numerous causes can be categorized into three main groups: Muscle compression or trauma, nontraumatic/exertional muscle damage, and toxins. Rhabdomyolysis is a clinical diagnosis and imaging reflects the underlying cause and extent of muscle damage. Involved muscles typically display enlargement, edema, and hemorrhage.

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IMPORTANT SAFETY INFORMATION[3]

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- The risk for NSF appears highest among patients with:
  - Chronic, severe kidney disease (GFR < 30 mL/min/1.73m2), or
  - Acute kidney injury.
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
- For patients at highest risk for NSF, do not exceed the recommended DOTAREM dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.

INDICATIONS AND USAGE

DOTAREM® (gadoterate meglumine) injection is a prescription gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

CONTRAINDICATIONS

History of clinically important hypersensitivity reactions to DOTAREM.

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Anaphylactic and anaphylactoid reactions have been reported with DOTAREM, involving cardiovascular, respiratory, and/or cutaneous manifestations. Some patients experienced circulatory collapse and died. In most cases, initial symptoms occurred within minutes of DOTAREM administration and resolved with prompt emergency treatment.
- Before DOTAREM administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to DOTAREM.
- Administer DOTAREM only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.
- Gadolinium Retention: Gadolinium is retained for months or years in several organs. The highest concentrations have been identified in the bone, followed by brain, skin, kidney, liver and spleen. The duration of retention also varies by tissue, and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs.
- Consequences of gadolinium retention in the brain have not been established. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention.
- Acute Kidney Injury: In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging.
- Extravasation and Injection Site Reactions: Ensure catheter and venous patency before the injection of DOTAREM. Extravasation into tissues during DOTAREM administration may result in tissue irritation.

ADVERSE REACTIONS

- The most common adverse reactions associated with DOTAREM in clinical trials were nausea, headache, injection site pain, injection site coldness and rash.
- Serious adverse reactions in the Postmarketing experience have been reported with DOTAREM. These serious adverse reactions include but are not limited to: arrhythmia, cardiac arrest, respiratory arrest, pharyngeal edema, laryngospasm, bronchospasm, coma and convulsion.

USE IN SPECIFIC POPULATIONS

- Pregnancy: GBCAs cross the human placenta and result in fetal exposure and gadolinium retention. Use only if imaging is essential during pregnancy and cannot be delayed.
- Lactation: There are no data on the presence of gadoterate in human milk, the effects on the breastfed infant, or the effects on milk production. However, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is present in breast milk.
- Pediatric Use: The safety and efficacy of DOTAREM at a single dose of 0.1 mmol/kg has been established in pediatric patients from birth (term neonates ≥ 37 weeks gestational age) to 17 years of age based on clinical data. The safety of DOTAREM has not been established in preterm neonates. No cases of NSF associated with DOTAREM or any other GBCA have been identified in pediatric patients age 6 years and younger.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.
Please see the full Prescribing Information, including Boxed Warning and the patient Medication Guide, for additional important safety information.

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- Many pediatric hospitals have or plan to switch to Dotarem, a stable macrocyclic GBCA[5]
- The only imaging contrast with a macrocyclic and ionic structure for high thermodynamic and kinetic stability[1,2]
- Following repeated administration, no visible T1 signal intensity detected on non-contrast images within the brain[6-10]

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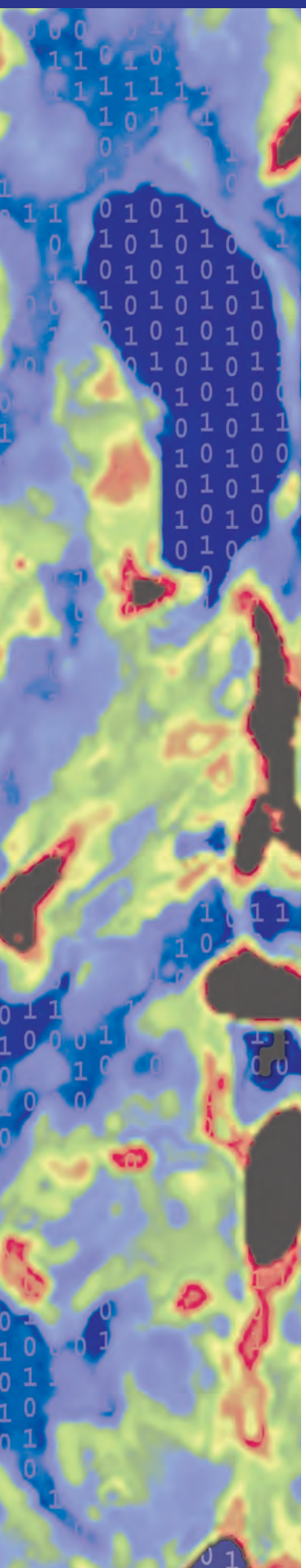

A Call for Radiology-led Innovation

Amine Korchi, MD

Radiologists owe a large share of their success to non-radiologists.

From the discovery of X-rays by Wilhelm Röentgen in 1895 through the introduction of CT and MRI in the 1970s and '80s, radiologic innovation was characterized largely by advances in imaging hardware and operating systems and essentially driven by physicists, chemists, and engineers.

Radiologists were mostly users of these breakthrough technologies and contributors to their clinical application.

But since the introduction of radiology information systems (RIS) and picture archiving and communication systems (PACS) during the '80s, radiologists and technologists have gradually become more involved in the development of these tools, which are highly physician-centric and strongly intertwined with clinical workflows.

In 1980, American academics and private hospitals created the Radiology Information Systems Consortium (RISC), whose aim was to develop a new RIS that would serve the needs of medical imaging. The RISC issued a request for proposal seeking help from an industrial and technical partner. The Digital Equipment Corporation (DEC), which already had earned a reputation for its innovative technology, funding, industrial know-how, and close collaboration with user groups and healthcare professionals, won the contract.

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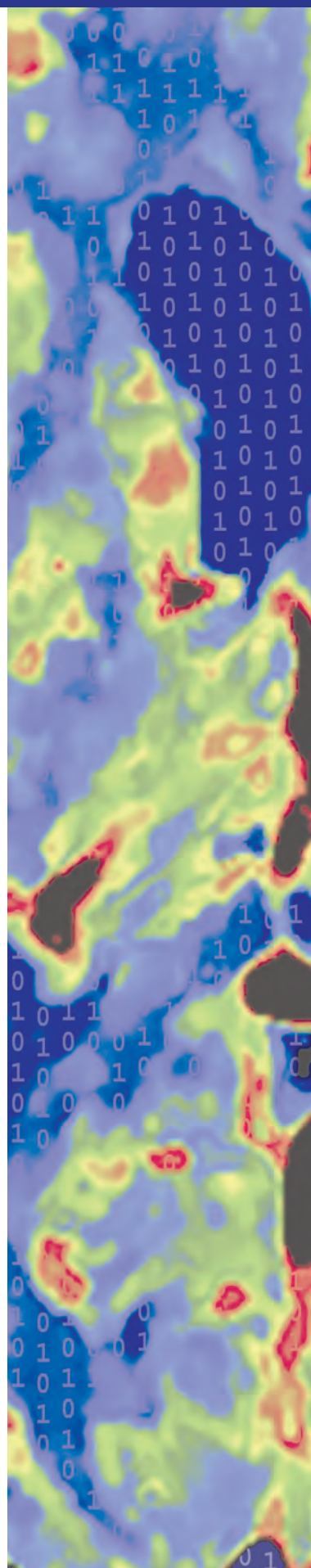
The radiology-led collaboration between the RISC and DEC went on to open the way to the development of new RIS software that earned fast adoption in radiology thanks to its ability to address the specific needs of medical imaging practitioners.

In a way, DEC is the ancestor of today's startups. The company was founded in the 1950s by two engineering students working at the Massachusetts Institute of Technology's Lincoln Lab who believed that transistor-based computers would revolutionize the corporate world with smaller, faster, cheaper, and more efficient machines than the bulky and expensive IBM computers available at the time.

While looking for investors to fund the company's early stages of development, the two entrepreneurs were advised to avoid using the word "computer" in their presentation because an article had just recently appeared in *Fortune* magazine stating that no monetization should be expected from the nascent computer industry.

Yet, in 1957, a private equity firm named ARD made a $70,000 equity investment for 70% ownership of the newly formed company. DEC went public in 1966, became a Fortune 500 company in 1974, and was acquired by Compaq in 1998. It was one of the largest acquisitions in computer industry history, and DEC today is recognized as the first home run of venture capital (VC) funding.



One hand cannot clap; Collaboration is a sine qua non *to innovation.*

Nowadays, a wide ecosystem of VC-backed artificial intelligence (AI) startups is transforming the way medical images are produced, processed, and interpreted. But even though AI is recognized as the next driver of radiologic progress, the "killer" AI application with a viable business model in this field still has not been found.

In the previously mentioned collaboration between RISC and DEC, the breakthrough of the partnership lay in the fact that innovation was requested and guided by hospitals in order to enhance their workflows.

And because radiology AI research and development depends heavily on radiologist and technologist know-how, these clinicians have the legitimacy to become leading actors of the AI-based transformation by enabling development of truly useful solutions and improving capital spending efficiency.

To build a sound AI product in radiology, six prerequisites should be met: a clinical need must be identified with granularity, relevant data must be queried and collected, medical images must be prepared and annotated, models must be validated and tested, user interfaces must be built, and software must be integrated into existing IT infrastructure and workflow.

Each of these steps requires deep domain expertise and clinical insights that are mainly in the hands of healthcare professionals. Therefore, it is clear that these stakeholders are best qualified to lead and orchestrate AI development in radiology.

Obviously, most medical imaging clinicians and professionals do not have the technical or industrial skills to bring AI software to market. One hand cannot clap; collaboration is a *sine qua non* to innovation. Partnerships with startups and manufacturers are the right approach, and while they are already forming, they are not headed in the right direction.

Today's most innovative ideas continue to emanate from startups. It is their AI engineers or computer scientists who knock on the door of hospitals to beg for data and insights, when it should be healthcare professionals knocking on their doors and looking for their expertise.

For the sake of more constructive and useful outcomes, radiology departments and healthcare institutions should take ownership of the innovation process. They need to adopt the right mindset by identifying their own needs, auditing and preparing their own data, allocating protected time and resources to their own research and co-development, and most importantly, creating their own governance and frameworks to facilitate collaboration with the external world.

Moreover, healthcare professionals and institutions must educate themselves in the workings of the non-medical fields. A high-level understanding of AI technology will facilitate collaboration with technical and industrial partners; becoming familiar with innovation methodologies will enable them to take a structured approach to efficiently orchestrate innovation from ideation to product.

There can be no doubt: Without strong leadership from radiology in 2021 and the years to come, artificial intelligence will not be able to fully deliver on its promise to transform the field of medical imaging.

Nuclear Medicine Prepares for Greater Ga 68 Demand

Mary Beth Massat

When the US Food and Drug Administration (FDA) approved the use of gallium 68 prostate-specific membrane antigen (PSMA)-11 (Ga 68 PSMA-11) PET imaging for prostate cancer in December, nuclear medicine specialists were not the only ones excited by the development.

Several companies aligned with the production and supply chain for Ga 68 had been anticipating—and planning for---the FDA's approval and its subsequent expected impact on demand for Ga 68, which can be used diagnostically when paired with PSMA-11, and therapeutically when paired with lutetium-177 or actinium -225.

"We made the investment in a GMP 68 Ga generator years before any drugs were approved, betting that the market was going to have a 68 Ga drug," says Jay Simon, general manager and managing director of Eckert & Ziegler Radiopharma (Berlin).

In its action, the FDA gave the University of California, San Francisco (UCSF) and University of California, San Diego (UCSD) approval to label the Ga 68 isotope with PSMA for PET Imaging of the prostate.

Researchers reported that clinical trials comparing PSMA PET imaging with 18F fluciclovine PET found that Ga 68 PSMA-11 PET detected significantly more prostate lesions than 18F fluciclovine PET imaging in cases of cancer recurrence following prostatectomy.[1] Peter Carroll, MD, a professor at the UCSF Helen Diller Family Comprehensive Cancer Center, called the development a "game changer" in a statement issued by UCSF.

In addition, there are nearly 400 clinical trials[2] currently underway involving the use of Ga 68 for both diagnosis and therapeutics for prostate, neuroendocrine tumors and other types of cancer. "The market is definitely growing, even beyond PSMA," says Lutz Helmke, PhD, Head of the Medical Radiopharma Segment at Eckert & Zeigler. "We believe there are many more tracers that will come to market and, therefore, we have done our utmost to increase capacity for this product."

Dr Helmke adds that after the 2017 shortage of germanium, which is used to make Ga 68**,** Eckert & Ziegler further increased its generator production capacity. He believes the company can meet current world demand for Ga 68 generators; however, he said the company is also preparing for the increase in demand resulting from the anticipated regulatory clearance of Ga 68 PSMA-11 for general clinical use and will be looking for additional suppliers for its GMP grade germanium.

Dr Helmke says there is a trend in the US toward developing larger Ga 68 generators with higher activities, from 50 mCi to 100 mCi. Eckert & Ziegler has developed a higher activity/higher capacity generator and will be filing for FDA approval in the near future. The company has also opened a new production facility in the Boston area.

"We have a geo strategy to serve our clients regionally but more importantly, we will have CMO capabilities so we can produce our customers final product," Dr Helmke says.

Raw Material To Generator Development

IRE ELiT (Fleurus, Belgium), a division of IRE, is also taking action to increase its production of germanium and Ga 68. With respect to the former, IRE is building its own cyclotron to produce germanium; it is also working to increase production of Ga 68 generators and higher-quality and capacity Ga 68—up to 100 mCi.

"This is very important for us to have an independent source of germanium," says Jean Bonnet, IRE's head of strategy, sales, and marketing. "We expect that in the future there will be intense competition to source germanium due the anticipated increase in demand for

Ms Massat is a contributing editor to Applied Radiology.

Ga 68 generators. This will preserve our independence and capacity to maintain our position in the future market."

The higher-capacity generators will offer more flexibility than 50 millicurie generators, Bonnet says.

"We know there will be a burst of demand for several months when there is approval for a new indication, such as with Ga 68 PSMA PET," Bonnet says. "So we are preparing for this flexibility with our partners."

Made in the USA

In 2018, after four years as a US distributor of Ga 68 generators for German-based Isotopen Technologien München AG (ITM), RadioMedix (Houston, TX) began preparing to manufacture its own Ga 68 generators, making it the only US manufacturer of the generators, says Ebrahim S Delpassand, MD, CEO, founder and chairman of the board.

"Our plan was to … increase the bandwidth, or output, of the Ga 68 generators," Dr Delpassand says. "This was in anticipation that Ga 68 usage will only increase."

A secondary goal was to help ITM file a drug master file (DMF) in the US, which occurred in June 2020 for ITM's next generation Germanium-68/Gallium-68 (^{68}Ge/^{68}Ga) generator, GeGant. GeGant generators are available in 30, 50, and 100 mCi.

"Now we have the capability to manufacture five generators every day. This is a significant for generator accessibility in the market," Dr. Delpassand says. "We don't anticipate any shortage of Ga 68 supply in the market for PSMA, or for future Ga 68-labeled agents that will come to market."

Dr. Delpassand sees other opportunities to label Ga 68 with different ligands to address unmet needs in oncology, including targeted therapies for brain tumors, ovarian cancer, pancreatic adenocarcinoma and triple negative breast cancers.

A Solid Approach

Although Ga 68 is generally produced in generators, ARTMS (Burnaby, British Columbia) has developed a low-energy cyclotron, QUANTM Irradiation System (QIS), to produce Ga 68 from solid zinc-68 targets. ARTMS CEO Charles Conroy explains that the QIS is used to produce decentralized radiopharmaceuticals such as Ga 68 on-site at hospitals, radiopharmacies, universities, and the like. The QIS is compatible with existing and new cyclotrons.

"There are hundreds of cyclotrons in North America, and with the QIS we can get the production closer to the end user," says Conroy. "Additionally, we can create large volumes of radioisotopes by utilizing high-purity, solid-metal targets that are then irradiated, significantly amplifying the amount of Ga 68 that one can produce. Using that solid target, a non-radioactive material, and a process that results in fewer impurities gives us the ability to produce such large quantities without the need for a generator. Its completely different than what is on the market today."

Compared to Ga 68 generators that typically produce 50-100 mCi of Ga 68, Conroy says the QIS can produce five curies each hour, enough for almost 100 patients. In December 2020, ARTMS received Health Canada clearance to use QIS to produce technetium-99m. The QIS can also perform a "split" run, where the beam can be used to make both copper and Ga 68, for example, on a single production run.

"With the QIS, we are able to create enough material in one location, which would usually be a commercial radiopharmacy, to diagnose or treat patients across several different cities," Conroy adds.

"Our customers are really delighted that ARTMS technology gives them more supply chain control and enables them to treat more patients from product being supplied from a single site Conroy says.

In early January, ARTMS and Telix Pharmaceuticals (Melbourne, Australia) announced the successful preparation of Telix's TLX591-CDx (illumet™), a radiopharmaceutical cold kit containing the components needed to prepare Ga 68-PSMA-11 at ambient temperature. The kit is being evaluated at several institutions in the US, including Emory University Hospital, Memorial Sloan Kettering Cancer Center, City of Hope, and Endocyte (Novartis). Further, Telix has established a network of US partners, including approximately 100 nuclear pharmacies, to prepare and distribute the kits for investigational use in qualified clinical trials.

"We anticipate every corner of America, Europe or any country we serve will be able to offer prostate imaging to their patients," says Telix CEO Chris Behrenbruch. It doesn't matter if it's a New York-area hospital or a hospital in a remote area, everybody's going to have access to this diagnostic technology."

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Localized Prostate Cancer Recurrence

R. Jeffrey Karnes, MD, FACS; Mohamed E. Ahmed, MBBCh

Affiliation: Department of Urology, Mayo Clinic, Rochester, MN.

CASE SUMMARY

A 70-year-old man presented with persistent rising prostate specific antigen (PSA) of 3.2ng/mL in July 2020. The patient was post retropubic radical prostatectomy (RRP) for Gleason 3+4=7 in 2006. Subsequently, the patient experienced biochemical recurrences for which he received salvage external beam radiation therapy to the prostate bed in 2007, cryotherapy to the vesicourethral anastomosis in 2015, and external beam radiation therapy to the pelvic lymph nodes in 2016, followed by hormone therapy for approximately one year. In February 2019, the patient's PSA level started to rise to detectable levels at 0.45ng/mL, reaching 1.1ng/mL in July 2019.

A PET/MR scan revealed increased uptake in a perirectal lymph node. In September 2019, the patient underwent MRI-guided cryoablation of this perirectal lymph node. Interestingly, despite treatment, the PSA continued to rise to 2.3 ng/mL in March 2020, and to 3.2 ng/mL in July 2020.

The patient underwent evaluation with MRI of the abdomen and pelvis, C-11 choline PET/CT scan, and Ga-68 PSMA PET/CT scan.

IMAGING FINDINGS

MRI of the abdomen and pelvis revealed a post-ablation defect in the left posterolateral aspect of the vesicourethral anastomosis. However, there was prominent increased signal that could not exclude recurrent tumor in this region. In addition, there was increased activity around the ablated left perirectal lymph node. There were multiple tiny lymph nodes worrisome for nodal metastases within the perirectal and presacral regions. Additionally, there was a 3-mm right internal iliac chain lymph node also worrisome for metastatic involvement.

C-11 choline PET/CT scan revealed a left presacral soft tissue nodule with trace choline uptake. There was no definite choline uptake above background activity along the vesicourethral anastomosis; however, the area was partially obscured by physiologic activity of urine. There was no other choline-avid lymphadenopathy or osseous or visceral metastases.

Ga-68 PSMA PET/CT scan, in comparison, revealed multiple small posterior and left lateral perirectal tracer-avid lymph nodes or soft tissue nodules. There was also another tracer-avid anterior right perirectal soft tissue nodule or lymph node abutting the posterior aspect of the bladder just to the right of midline. In addition, there was intense tracer uptake at the vesicourethral anastomosis as well as minimal tracer activity in a right internal iliac lymph node. There were no tracer-avid bone lesions.

Of interest, both the MRI and C-11 choline PET/CT scan were suspicious for local recurrence as well as perirectal nodal recurrence, however, these lesions were very obvious on Ga-68 PSMA PET/CT scan.

DIAGNOSIS

Localized prostate cancer recurrence

FOLLOW-UP

The patient re-initiated treatment with Lupron hormone therapy of three months' duration. The patient responded very well to the treatment and the PSA decreased rapidly to undetectable levels <0.10ng/mL in one month.

DISCUSSION

Prostate cancer accounts for nearly 33,000 deaths annually, representing the second-most common cause of cancer death among men, ranking only behind lung cancer.[1] While primary prostate cancer can be managed with radical prostatectomy or radiation therapy, 40% of patients will experience disease relapse.[2] Recurrent prostate cancer requires personalized management that depends on the location of disease relapse. In 2013, the US Food and Drug Administration approved C-11 choline PET/CT scanning for detecting prostate cancer relapse after primary treatment failure, with an optimum PSA level of ≥ 2.0ng/mL.[3] Despite the higher sensitivity of the C-11 choline PET/CT scan to disease recurrence compared with conventional imaging, Ga-68 PSMA PET/CT has demonstrated significantly higher sensitivity than C-11 choline PET/CT. In a systematic review

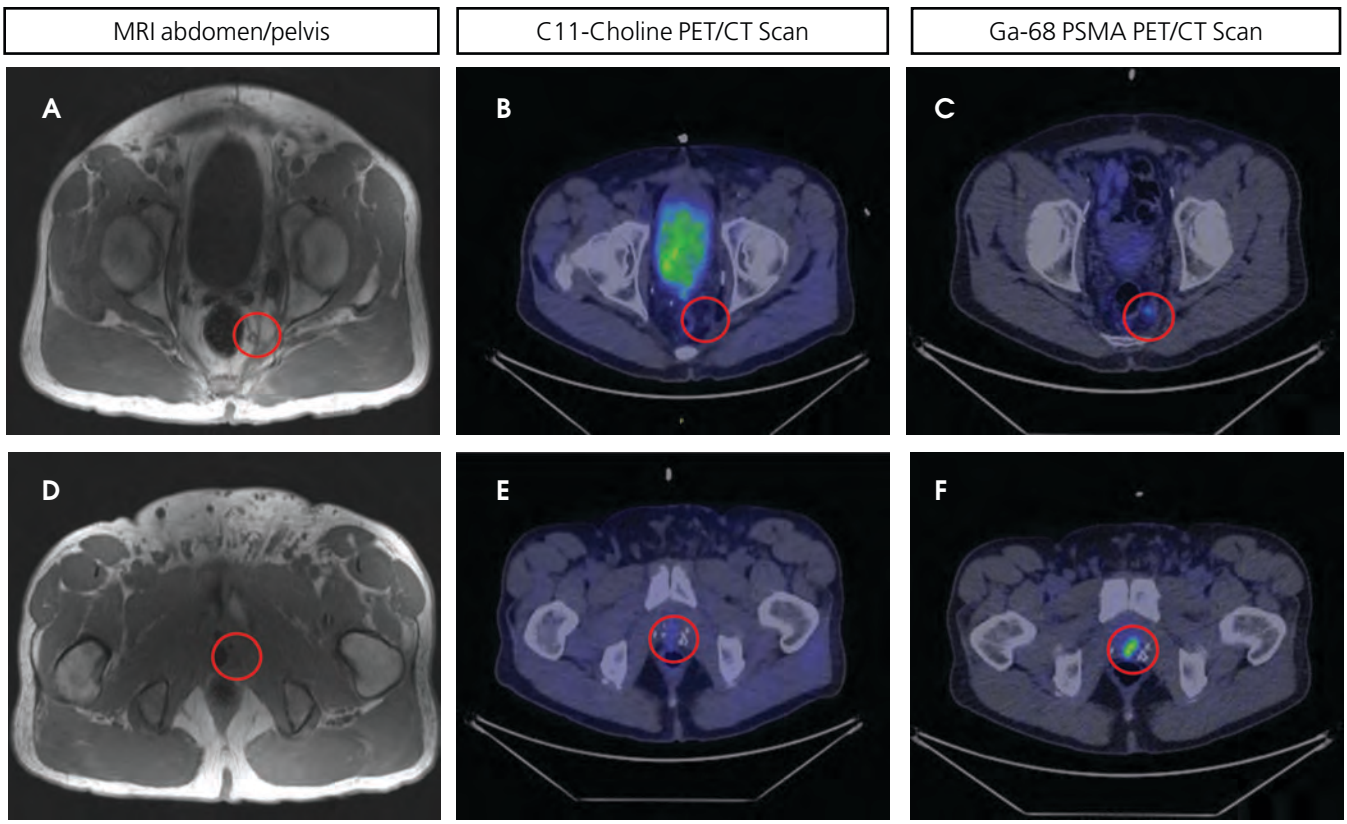

FIGURE 1. *Comparison between MRI abdomen/pelvis, C-11 choline PET/CT and Ga-68 PSMA PET/CT in detecting local recurrence.*

and meta-analysis, Eyben et al reported that Ga-68 PSMA PET/CT was able to detect the location of disease relapse after primary radical prostatectomy in half of patients with PSA levels between 0.5 and 1 ng/mL, and in up to 75% of patients with PSA >1 ng/mL.[4,5] Some recent reports suggest that Ga-68 PSMA PET/CT can detect disease recurrence at PSA levels <0.5 ng/mL.[6,7]

This report demonstrates the significant difference in sensitivity between MRI abdomen/pelvis, C-11 choline PET/CT, and Ga-68 PSMA PET/CT in detecting prostate cancer relapse. The higher sensitivity of Ga-68 PSMA PET/CT allows it to detect disease relapse at very small volumes of <8 mm.[8] Despite the fact that Ga-68 PSMA PET/CT is not yet approved by the FDA for this indication, Afaq et al reported that PSMA PET/CT has a significant impact on disease management, with overall changes in 39-76% of cases.[8] The high performance of PSMA PET/CT represents the future of prostate cancer diagnosis and management.

CONCLUSION

This report confirms the important clinical consideration of the high sensitivity of Ga-68 PSMA PET/CT in determining disease recurrence after initial treatment failure, particularly in patients with very low PSA levels.

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Alveolar Capillary Dysplasia with Misalignment of Pulmonary Veins

Anas Maatough; Richard B Towbin, MD; Mantosh Rattan, MD; Alexander J Towbin, MD

CASE SUMMARY

A 3-year-old with a history of imperforate anus and a one-day history of congestion, oxygen desaturations, and intermittent tachypnea presented with pulmonary hypertension and interstitial lung disease. Physical exam was nonspecific with tachypnea, mild subcostal retractions, and clear lungs bilaterally.

IMAGING FINDINGS

Chest CT revealed diffuse ground-glass pulmonary opacities with peripheral upper lung sparing (Figure 1). An echocardiogram revealed moderate dilation of the main pulmonary artery, moderate dilation of the right ventricle, and an elevated right ventricular pressure; however, the left ventricle was normal in size.

DIAGNOSIS

Alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV). Differential diagnosis includes idiopathic persistent pulmonary hypertension and congenital cardiopulmonary disease with pulmonary hypertension.

DISCUSSION

Alveolar capillary dysplasia with misalignment of pulmonary veins is a rare, congenital disease with fewer than 200 cases reported.[1] MacMahon first described the condition in the literature in 1948, reporting three infants, born full-term, who developed respiratory distress and cyanosis. Autopsy revealed stromal dysplasia and decreased alveolar air space.[2] Since then, reports of ACD/MPV have increased with improved characterization of clinical features and pathology, but the pathogenesis and genetics of the disease remain unclear.

Patients with ACD/MPV typically develop respiratory distress, severe pulmonary hypertension, and cyanosis in the first 24-48 hours of life, with high probability of mortality in the first month.[3] However, there have been a few reported cases of infants presenting with ACD/MPV beyond the neonatal period, with more suspected being unreported, owing to the need for biopsy or autopsy for diagnosis.[4]

In this case, lung biopsy revealed patchy features of lobular underdevelopment, concentric medial muscular hypertrophy, areas of deficient capillaries and poor apposition, as well as areas of near-normal capillary profiles, abnormal artery/vein pairing, extension of mural smooth muscle into distal acinar vessels, and dilation of the lymphatic vessels.

Patients with delayed ACD/MPV tend to present with mild or absent tachypnea at birth but may remain asymptomatic for months or years. One report suggests that viral infections may trigger a pulmonary hypertensive crisis in delayed-onset patients, owing to the abnormal pulmonary vasculature.

Systemic abnormalities may also be present with ACD/MPV. Concurrent gastrointestinal and urogenital abnormalities, including anal atresia and redundant colon, occur in 50-80% of ACD/MPV patients.[1] Treatment is limited, with only transient or no response to nitric oxide, pulmonary vasodilators, or extracorporeal membrane oxygenation (ECMO); as in this case, lung transplant is the only effective form of treatment.[4]

Imaging, such as echocardiography, can be helpful for excluding differential diagnoses such as congenital heart disease that may explain pulmonary hypertension. Diffuse ground-glass attenuation on chest radiography in neonates and chest CT beyond the neonatal period are often seen in ACD/MPV, but imaging can also appear normal.[1]

Histological examination of a lung biopsy is the gold standard for diagnosing ACD/MPV. Common histological findings include medial hypertrophy of pulmonary arteries and muscularization of arterioles, decreased number of capillaries, immature lobular development, and malposition of pulmonary veins adjacent to small pulmonary arteries.[5] The constellation of these histological findings is diagnostic for ACD/MPV. Lymphangiectasis has additionally been reported to be associated with ACD/MPV.[7]

Variations in histology may explain milder forms of ACD/MPV. One report correlates survivorship of ACD/

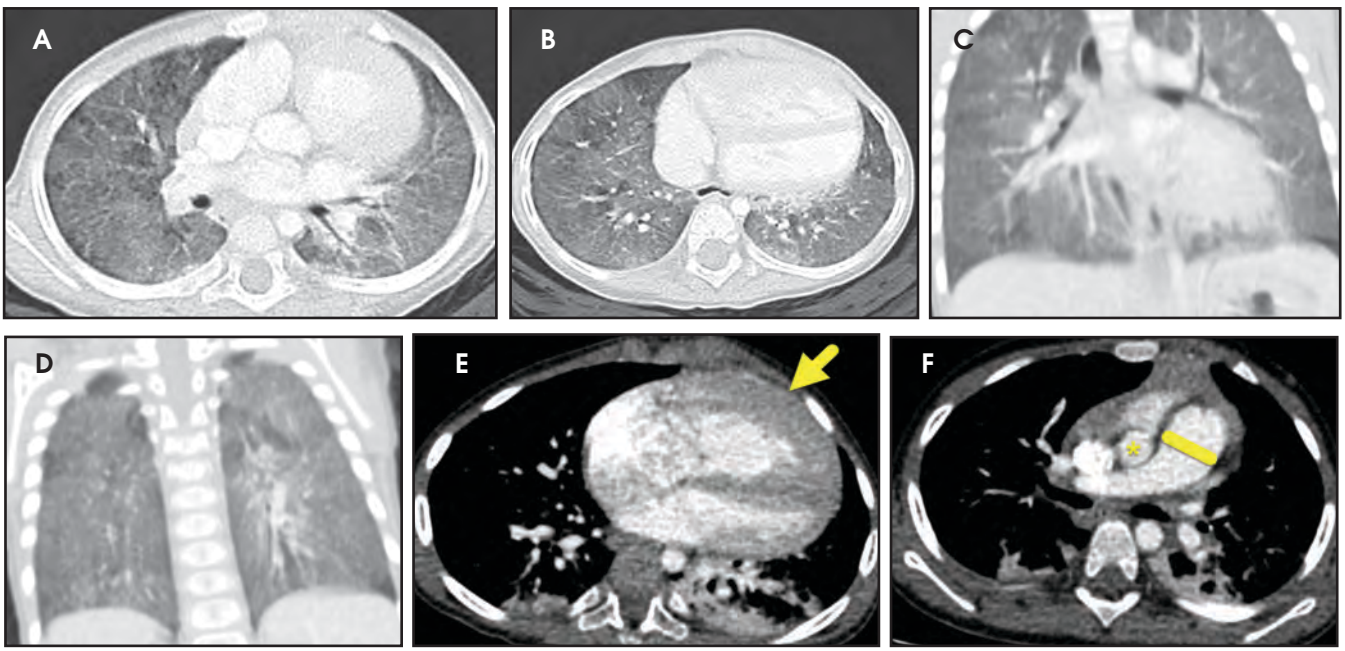

FIGURE 1. *Axial (A,B) and coronal (C, D) chest CT scans in lung window show diffuse, patchy ground-glass opacity with relative sparing at the periphery and anterior superior aspect of both lungs. Minimal intralobular septal thickening is present. Soft-tissue windows highlight right ventricular hypertrophy (E, arrow) and pulmonary artery hypertension with enlargement of the main pulmonary artery (F, line) in relation to the ascending aorta (*).*

MPV patients with increased capillary density and apposition to the alveolar epithelium.[5] Ito has also noted a correlation of patchy capillary reduction and abnormal alveolar air space, with delayed clinical presentation; his findings are consistent with previous findings in the literature. The presence of normal lung tissue bilaterally on imaging is also associated with a milder phenotype.[4]

The genetics of ACD/MPV remain unclear, as 60% of affected patients have no known cause. However, in 40% of patients, mutations in the *FOXF1* gene or microdeletions of 16q24.1-containing the *FOX* transcription gene cluster- have been associated with ACD/MPV. *FOXF1* is expressed in muscle cells of the lung and has been implicated with pulmonary vascular abnormalities in a murine model.[1]

Differential diagnosis includes idiopathic persistent pulmonary hypertension, which can be excluded as it typically completely resolves with respiratory interventions, including ECMO or pulmonary vasodilators.

CONCLUSION

ACD/MPV should be considered in patients who present with pulmonary hypertension with little improvement from respiratory interventions. While classically a neonatal disease, milder forms of the disease can present beyond the neonatal period. Histological examination of lung biopsy with the constellation of features described above is considered diagnostic; imaging is useful for supporting the diagnosis during work-up. Genetic testing may also be helpful for discerning heritable forms of the disease.

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APPLIED RADIOLOGY
RADIOLOGICAL CASE

Gorham-Stout Syndrome

Aynur Turan, MD; Pınar Çeltikçi, MD; Meltem Ozdemir, MD; Azad Hekimoglu, MD; Huseyin Coskun, MD

CASE SUMMARY

A 53-year-old was evaluated for right proximal upper extremity pain and progressive limitation of shoulder joint movement over a period of six years. The patient had type 2 diabetes mellitus. There was no fever, history of trauma, or any other disease. All blood testing was normal, including alkaline phosphatase. Clinical examination and other imaging methods identified no neurological or vascular etiology.

IMAGING FINDINGS

Anteroposterior radiography of the right shoulder demonstrated absence of the humeral head with tapering of the remaining bone tissue. There were accompanying millimeter-sized bone fragments in the adjacent soft tissue (Figure 1). Coronal T2 fat-saturated magnetic resonance imaging (MRI) revealed humeral head loss with prominent medullary bone edema in the metaphysodiaphyseal portion of the humerus and glenoid (Figure 2). These bone segments and the surrounding soft tissue enhanced markedly following intravenous contrast administration. MRI also showed increased joint fluid and signs of synovitis. Histopathological evaluation was reported as nonspecific proliferative, inflammatory disease.

DIAGNOSIS

Gorham-Stout syndrome (GSS)

DISCUSSION

Gorham-Stout syndrome, which is also referred to as "vanishing bone disease," is a rare disorder characterized by the disappearance of one or more bones. Etiopathology of this disease is unclear. Research suggests the condition arises from nonmalignant proliferation of hemangiomatous or lymphangiomatous tissue, resulting in progressive destruction and absorption of the affected bone.[1,2] One or more bones, most commonly the skull, upper and lower extremities, spine, and pelvic bones, may be affected.[2] Gorham-Stout syndrome has been reported in the literature as occurring most commonly in males up to 40 years of age; however, our patient did not fit these demographics.[2,3]

Clinical findings include pain, swelling, loss or restriction of motion, osseous deformity or, most frequently, bone fracture; rarely, GSS may be asymptomatic until late stages. Some related complications are respiratory dysfunction secondary to pleural effusion, chylothorax, osteomyelitis, and spinal cord lesions associated with vertebral bone involvement. [1,2]

Laboratory findings are almost always within normal limits, although alkaline phosphatase levels may be elevated. Imaging is usually the main diagnostic tool. Radiography initially reveals osteoporosis, followed by progressive fragmentation leading eventually to the entire loss of cortical bone in the late period. Computed tomography (CT) and MRI also demonstrate these findings in addition to diffuse atrophy of adjacent muscles owing to bone resorption.[2,3]

Histopathological findings of GSS are nonmalignant hyperproliferation of small vascular structures and progressive bone resorption.[4] The differential diagnosis includes hereditary multicentric osteolysis, osteolysis due to other diseases such as malignancy, hyperparathyroidism, syringomyelia, and tabes dorsalis.[2]

Treatment options include radiotherapy, alpha 2b interferon, supportive nutrition and bisphosphonates.[1,2] Surgery, consisting of resection of the affected area and bone graft placement is another therapeutic approach.[4]

CONCLUSION

Gorham-Stout syndrome is a rare entity whose diagnosis is usually overlooked, leading to delays in therapy. It should be considered, especially in the evaluation of osteolytic lesions in typical locations. Although imaging plays

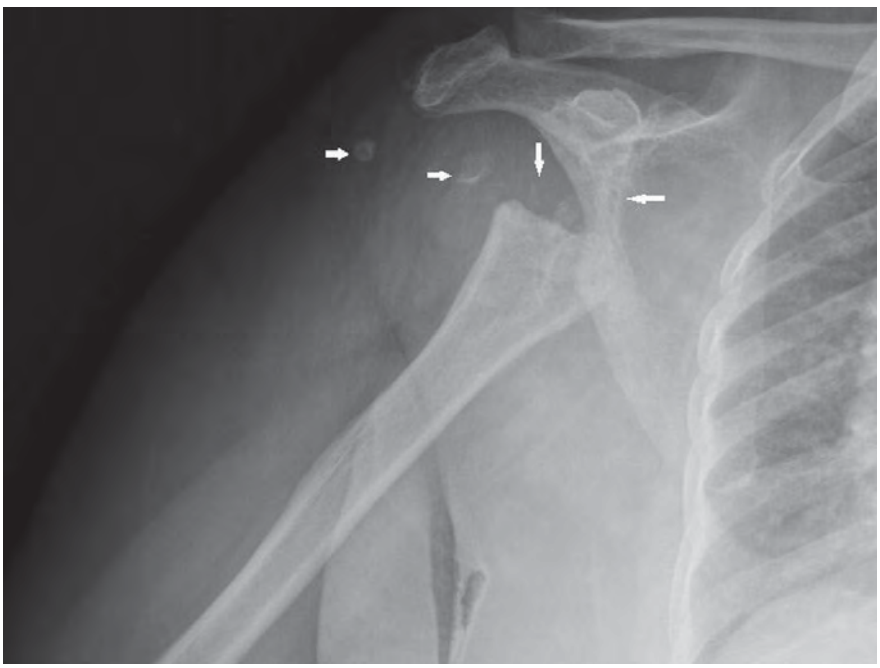

FIGURE 1. *A radiograph of the right shoulder shows absence of the humeral head (arrows) accompanied by millimeter-sized bony fragments in the adjacent soft tissues (arrows).*

an important role in GSS diagnosis, definitive diagnosis may be achieved by excluding other osteolytic causes in suspected cases.

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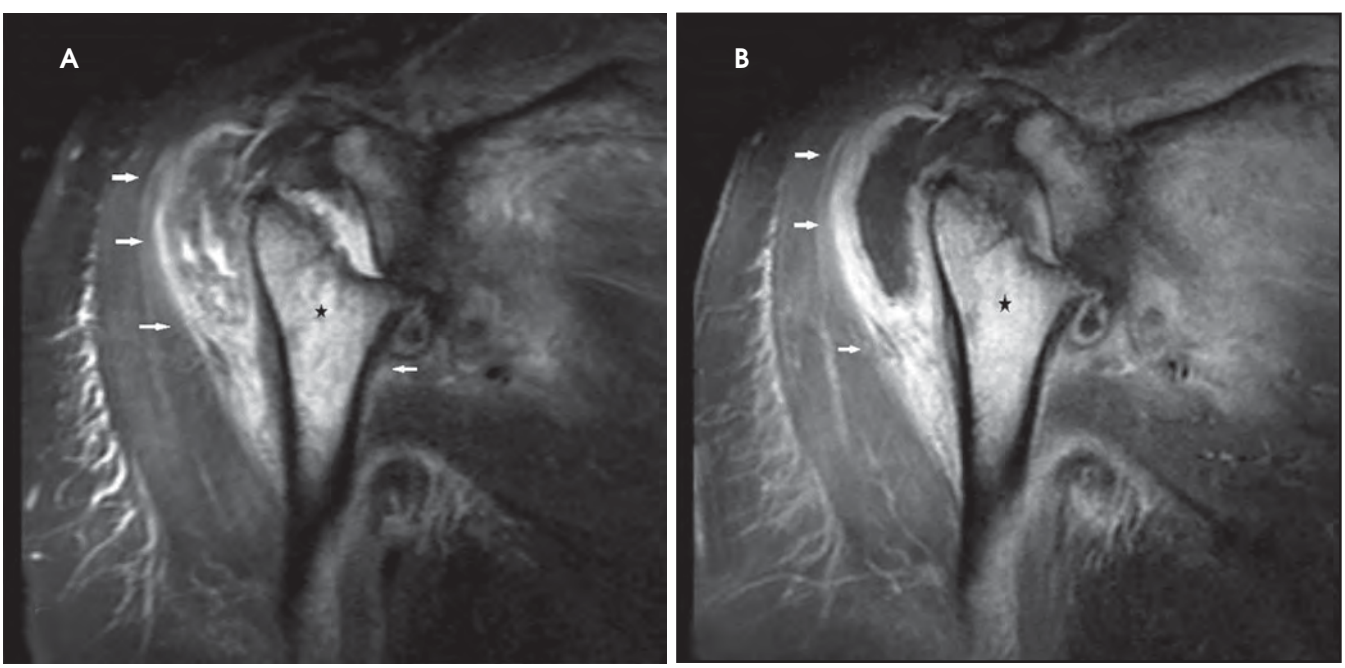

FIGURE 2. *(A) Coronal T2 fat-saturated MRI demonstrates loss of the humeral head with accompanying medullary bone edema in the proximal part of the humerus and glenoid (star). Surrounding soft tissues are edematous (arrows). (B) The remaining humeral portion (star). and surrounding soft tissues enhance markedly on T1 fat-saturated, contrast-enhanced MRI (arrows).*

Applied Radiology®
RADIOLOGICAL CASE

Primary Hepatic Neuroendocrine Carcinoma

David M Ban, MD; Paul Koscheski, MD

CASE SUMMARY

Primary neuroendocrine tumor of the liver is an exceedingly rare entity and is difficult to distinguish from other hepatic tumors based on radiographic findings. We report the case of a patient followed over a period of 3 years for a lesion in the left hepatic lobe. Upon hepatic lobe wedge resection, pathology revealed a primary hepatic neuroendocrine tumor.

IMAGING FINDINGS

A 71-year-old patient presented with right upper-quadrant abdominal swelling. MRI of the abdomen demonstrated a 1.5 cm lesion in the left liver lobe (segment 4A) that was hyperintense on T2 imaging, demonstrated early arterial enhancement without washout (Figure 1), and showed diffusion restriction. A follow-up MRI at 6 months showed no significant change in the lesion. Subsequent follow-up MRI two years after presentation demonstrated an interval increase in lesion size to 2.5 cm in diameter. At this time, the lesion contained mixed solid and cystic components with fluid-fluid levels (Figure 2). Multiphase CT of the liver the following year showed continued interval growth of the mixed solid and cystic lesion. At that time, the lesion measured 4.4 cm in diameter (Figure 3).

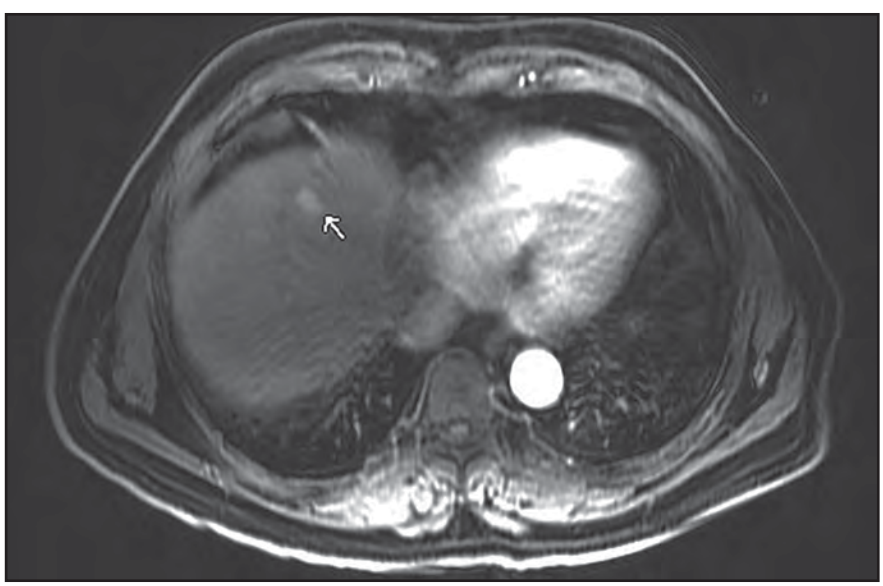

FIGURE 1. *Arterial phase contrast-enhanced MRI of the abdomen demonstrates 1.5 cm lesion in the left liver lobe (segment 4A) that is hyperintense on T2 imaging, demonstrates early arterial enhancement without washout, and shows diffusion restriction.*

The patient underwent evaluation for other primary malignancies. A CT of the chest, abdomen, and pelvis showed no evidence for other malignancy. Upper endoscopy was negative. Multiple polyps were discovered and several were biopsied during colonoscopy; none were malignant.

Suspicion for primary liver tumor or infection increased given the apparent absence of another primary malignancy. The patient was found to have an elevated serum chromogranin A level (204, subsequently 223; normal range: 25-140). Work-up for an infectious etiology, including *Echinococcus* Ab IgG EIA and *Entamoeba histolytica* IgG ELISA serologies, was negative. The elevated serum chromogranin A level raised suspicion for a neuroendocrine tumor. Subsequent nuclear medicine whole body octreotide In-111

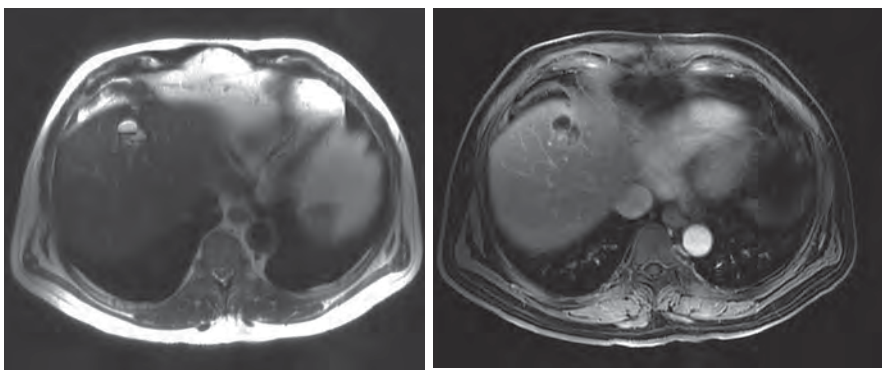

FIGURE 2. *Follow-up MRI demonstrates interval increase in lesion size to 2.5 cm in diameter with mixed contrast-enhancing solid components and cystic components with fluid-fluid levels on T2 (A) and post contrast T1 with fat-suppression (B).*

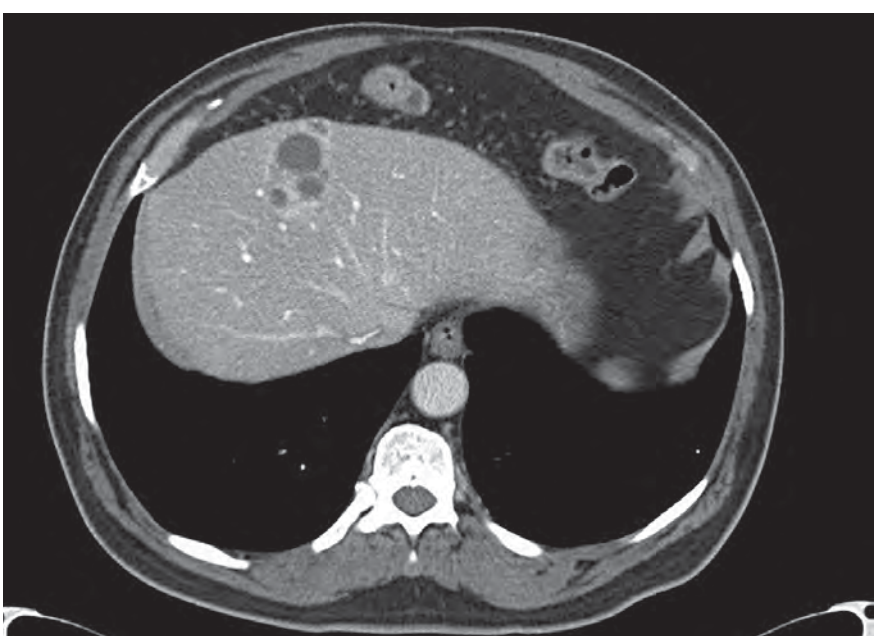

FIGURE 3. *Follow-up contrast-enhanced CT of the liver re-demonstrates the mixed solid and cystic nature of the lesion with continued interval growth.*

scan demonstrated focal increased radiotracer uptake in the liver, corresponding to the lesion seen on CT and MRI (Figure 4).

The patient underwent liver wedge resection. Immunohistochemical evaluation demonstrated positivity for chromogranin and synaptophysin markers, considered specific markers for neuroendocrine tumors.

DIAGNOSIS

Primary hepatic neuroendocrine carcinoma

DISCUSSION

Neuroendocrine tumors, which arise from neuroendocrine cells, are rare. They can arise in any organ that contains peptide and amine producing cells, but most occur in the gastrointestinal tract and lungs.[1] Diagnosis of neuroendocrine tumors is confirmed by pathology. Specific immunohistochemical markers include chromogranin A and synaptophysin. Octreotide imaging has a sensitivity up to 90% for neuroendocrine tumors.[2] Most of these tumors involving the liver

FIGURE 4. *Nuclear medicine whole body octreotide In-111 scan (A) demonstrates focal increased radiotracer uptake in the liver, corresponding to the lesion seen on coronal CT reformation (B).*

are metastases from another primary source. They tend to demonstrate strong arterial enhancement due to their vascularity.[3]

Primary hepatic neuroendocrine carcinoma (PHNEC) is an exceedingly rare entity, with only a few hundred cases reported in the literature.[4,5] PHNEC shows no strong gender predominance, but it tends to occur in patients aged 40-50 years.[6] PHNEC is often asymptomatic, or it may present with nonspecific symptoms such as abdominal pain, bloating, or jaundice.

Owing to the small number of reported cases, the imaging characteristics of PHNEC are not well defined and are difficult to distinguish from other primary tumors of the liver and metastases. Many reports have demonstrated cystic components on MRI and CT imaging,[5] similar to our case. In a case of suspected PHNEC, extrahepatic neuroendocrine tumors should be excluded with upper and lower endoscopy, as well as with CT and PET imaging.

Treatment of PHNEC depends on the location, aggressiveness, and presence of metastases. No staging guidelines currently exist for PHNEC. If it is confined to the liver, surgical resection must be considered. If the tumor is unresectable, transarterial chemoembolization is a potential treatment option. If metastases are present, chemotherapy is another potential management option; however, outcomes vary.[4]

There are currently no characteristic features to reliably differentiate PHNEC from other liver tumors. If PHNEC is suspected, serum markers, including chromogranin A levels, should be checked. Additionally, octreotide imaging can be obtained to assess the neuroendocrine nature of the tumor. A thorough investigation for an extrahepatic primary neuroendocrine tumor is necessary to exclude an etiology for metastasis, which is much more frequently encountered.

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RADIOLOGICAL CASE

A Rare Case of Lingual Thyroid in a Man

Dania Shakaroun, MD; Arti Bhan, MD; Dalal Ishani, MD

CASE SUMMARY

A 38-year-old man presented with a one-year history of constipation, cold intolerance, and pressure sensation in the lower neck. Physical exam revealed a normal appearance of the posterior wall of the oropharynx with no palpable thyroid gland. Thyroid-stimulating hormone (TSH) was 428 *u*IU/ml with undetectably low free tetraiodothyronine (FT4). Thyroid peroxidase antibodies were negative. An ultrasound scan of the neck, a contrast-enhanced CT (CECT) scan of the neck, and a thyroid I-123 scan of the neck were obtained.

IMAGING FINDINGS

The US showed an absence of thyroid tissue, while the thyroid I-123 scan showed an area of intense radiotracer uptake corresponding to a soft-tissue mass with some calcification posteriorly at the base of the tongue, anterior to the oropharynx at the level of the mandible consistent with lingual thyroid (Figure 1). The CECT showed a densely calcified, hyperdense, contrast enhancing mass in the midline involving the tongue base at the level of the foramen cecum measuring 1.5 cm x 1.2 cm x 1.5 cm with an associated small cystic component (Figure 2).

DIAGNOSIS

Lingual thyroid. Differential diagnoses include lingual thyroglossal duct cyst, lingual abscess, branchial cleft cyst, squamous cell carcinoma of the base of the tongue, and dermoid or epidermoid cyst.

DISCUSSION

Lingual thyroid refers to thyroid tissue at the level of the base of the tongue resulting from development abnormalities during embryogenesis. During the third week of gestation, the thyroid appears as a median diverticulum extending from the foramen cecum at the floor of the first and second pharyngeal pouches. This diverticulum then descends as the thyroglossal tract ventrally and caudally towards the position of the normal thyroid in the anterior neck by the seventh week of gestation. A complete failure of the gland to descend past the foramen cecum results in a lingual thyroid.[1]

Lingual thyroid, which represents 90% of all cases of ectopic thyroid, was first described in 1869 in a neonate experiencing upper airway obstruction.[2] It is a rare congenital anomaly with a prevalence rate between 1 in 100,000 and 1 in 300,000, and reported clinical incidence between 1:4000 and 1:10000.[3] Lingual thyroid has a significant female predominance; the female-to-male ratio is 4:1.[4] Very few cases of lingual thyroid have been described in male patients.

Lingual thyroids are largely asymptomatic, discovered either incidentally on routine exam or during postmortem studies. Symptoms are related either to clinical hypothyroidism, as in our patient, or to local symptoms from enlargement of the thyroid tissue. Evident hypothyroidism is found in 33% to 62% of patients with lingual thyroid.[3]

Regional symptoms and signs (dysphagia, dysphonia, dyspnea, hemoptysis, or foreign body sensation) are especially apparent with upper respiratory infections, pregnancy, and other conditions with increased dependence on thyroid hormone and subsequent tissue enlargement.[3] Unlike the predominance of papillary carcinoma in the orthotopic thyroid, follicular carcinoma is predominant in lingual thyroid.[5,6] Lingual thyroid medullary and anaplastic carcinoma have not been reported.

Multiple radiographic modalities, including ultrasound, scintigraphy, CT, and magnetic resonance imaging (MRI) can be used to diagnose lingual thyroid. Ultrasound of the neck is a noninvasive and cost-effective test that usually demonstrates absence of orthotopic thyroid tissue. A more thorough evaluation of the neck using a low frequency, curved transducer can reveal the size, location, and echogenicity of ectopic thyroid tissue.[7]

Miller described the sonographic appearance of lingual thyroid as a solid mass with smooth internal texture and low level echogenicity that is similar to normal thyroid parenchyma.[8] Thyroid scintigraphy, which utilizes one of the radioisotopes of iodine (usually I-123) or technetium-99m pertechnetate, is considered the modality of choice for identifying ectopic thyroid. It can detect

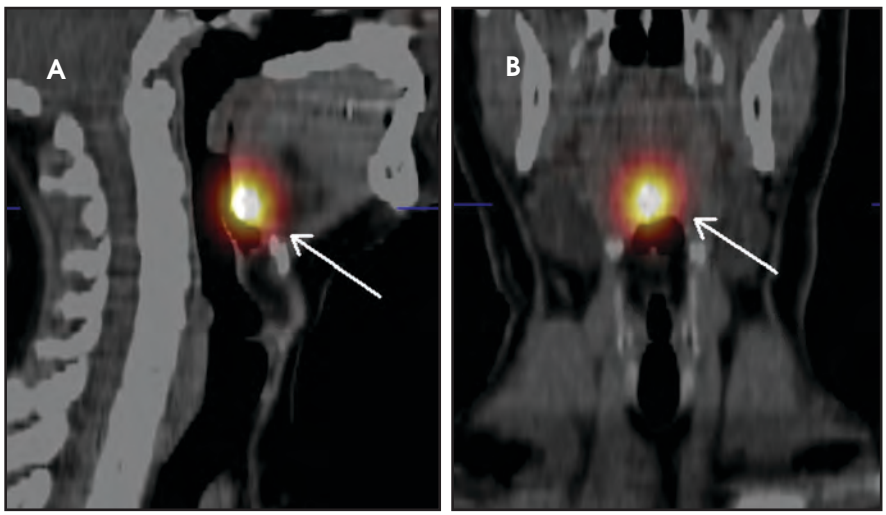

FIGURE 1. *Thyroid I-123 scan in the sagittal (A) and coronal (B) planes showing an area of intense radiotracer uptake (arrows) at the base of the tongue consistent with lingual thyroid*

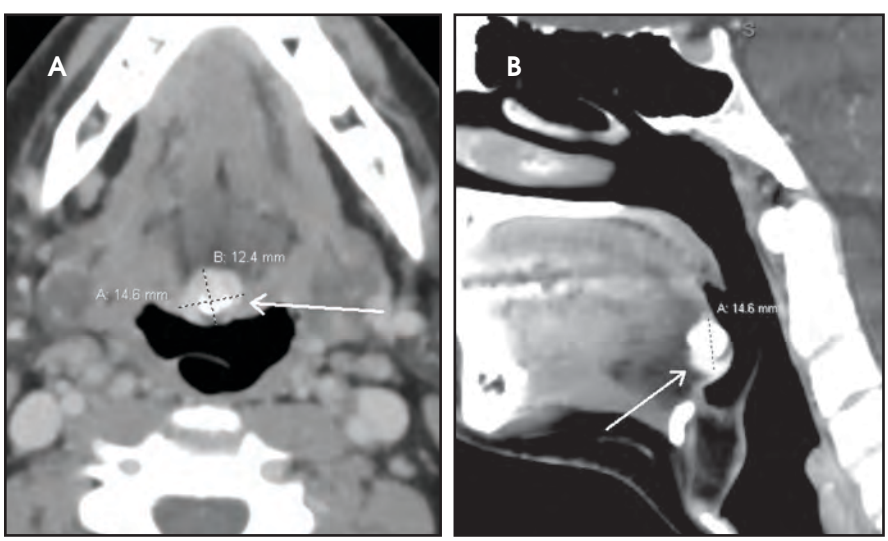

FIGURE 2. *CT of the neck in the axial (A) and sagittal (B) planes shows a hyperdense enhancing mass at the tongue base (arrows).*

the location, size, and level of activity of any orthotopic and ectopic thyroid tissue. CT and MRI can accurately define the extension and location of any glandular tissue.

Lingual thyroid management varies based on symptomatology and suspicion of malignancy. Asymptomatic and euthyroid patients can be monitored for possible complications. Hypothyroid patients or patients with a mildly enlarged gland causing minimal obstructive symptoms should be started on hormonal suppression therapy to relieve symptoms and reduce the size of the gland.[9]

Any suspicion of malignancy or the presence of major obstructive symptoms necessitate excision. Surgical removal of the mass can be attempted with an external approach such a trans-hyoid or lateral pharyngotomy, or by performing transoral surgical removal, a newer and safer technique.[4] Patients who are not surgical candidates can be treated with ablative radioiodine therapy.[10]

In our case, fine needle aspiration was not possible given the location of the tissue. The patient underwent transoral robotic lingual thyroidectomy owing to suspicion of malignancy, with the final pathological exam confirming the presence of thyroid tissue, which was negative for malignancy.

CONCLUSION

Lingual thyroid is a rare anomaly among male patients. A high level of suspicion should be present in the setting of clinical hypothyroidism and obstructive symptoms. It is important to note the different radiographic modalities that can be utilized and the different characteristic appearance of lingual thyroid in each study.

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Affiliation: Henry Ford Hospital, Detroit, MI. Disclosures: None

APPLIED RADIOLOGY
RADIOLOGICAL CASE

Mammary Myofibroblastoma in a Male Patient

Eslam Youssef, MD; RaeLynne MacBeth, MD; Xiaochen Liu, MD, BSBE; Lina Elsamaloty, MD; Dalia Ibrahim, MD; Haitham Elsamaloty, MD

CASE SUMMARY

A 68-year-old male presented with a 3-month history of a tender, palpable mass of the left breast in the 11 o'clock position. The patient had a history of prostate cancer, raising concern for metastatic carcinoma.

IMAGING FINDINGS

Diagnostic mammography revealed a high-density lesion with macrolobulated margins and without spiculated borders. Scattered calcifications were seen within the left breast. These findings were classified as BI-RADS 4 (suspicious finding). Focused ultrasound demonstrated an elongated hyperechoic mass with smooth margins measuring 2.3 × 1.2 × 2.0 cm. There was minimally increased color flow internally. Elastography revealed hard and soft areas within the mass.

Ultrasound-guided biopsy with a 14-gauge coaxial biopsy gun obtained four core biopsy samples. Pathology results classified the mass as a myofibroblastoma of the breast.

DIAGNOSIS

Mammary myofibroblastoma

DISCUSSION

Myofibroblastomas are uncommon, benign stromal tumors of the breast first described in 1987 by Wargotz, et al.[1] Pathologically, myofibroblastomas are described as "benign spindle cell tumors of the mammary stroma"' due to their derivation from stromal myofibroblasts commonly found in the breast parenchyma.[2] Genetically, they are thought to be correlated with the deletion of the 13q14 region, similar to other types of benign mesenchymal and stromal neoplasms.[2,3] Myofibroblastomas typically occur in older men and postmenopausal women; however, they can present at any age.[4] Although myofibroblastomas are most commonly found within the breast, there have been extramammary cases reported in the literature as well, including in the abdominal wall, the thigh, and even the tongue.[3,4,5-8]

These masses are typically unilateral, painless, and have the ability to slowly increase in size. The average size is between 1 and 4 cm; however, much larger dimensions have been reported in the literature.[9]

Mammographically, myofibroblastoma presents as a well-circumscribed mass without architectural distortion or suspicious calcifications.[4] They may also demonstrate microlobulated margins that can mimic breast carcinoma on mammography.[10] In this case, mammography showed scattered calcifications and a dense mass with macrolobulated margins.

Sonographically, there have been cases where a myofibroblastoma appeared as a circumscribed, slightly echogenic lesion with distal acoustic attenuation, as well as a circumscribed, slightly hypoechoic and non-attenuating lesion.[4] Its sonographic appearance may reveal ill-defined borders along with posterior shadowing, and a biopsy is recommended to distinguish it from other lesions.[11]

Differential considerations include, but are not limited to, primary breast carcinoma, fibroadenoma, gynecomastia and, more importantly in this case, metastatic carcinoma due to the patient's history of prostate cancer.

Surgical excision is recommended, although ultrasound and/or mammography may be performed every 6 months up to 2 years to confirm stability.[12] There have been no reports of malignant transformation; recurrence of myofibroblastoma after surgery is uncommon, likely owing to their smooth margins.

CONCLUSION

Myofibroblastoma of the breast is a rare, benign mass that is difficult to distinguish from other entities such as a benign fibroadenoma or carcinoma. It is more common in older males and postmenopausal females. Its appearance on mammography and ultrasound is inconclusive, and a core biopsy tissue sample is needed to confirm the diagnosis. Surgical excision is recommended; however, there have been no reports of malignant transformation. Follow-up studies may be performed for up two years to confirm stability.

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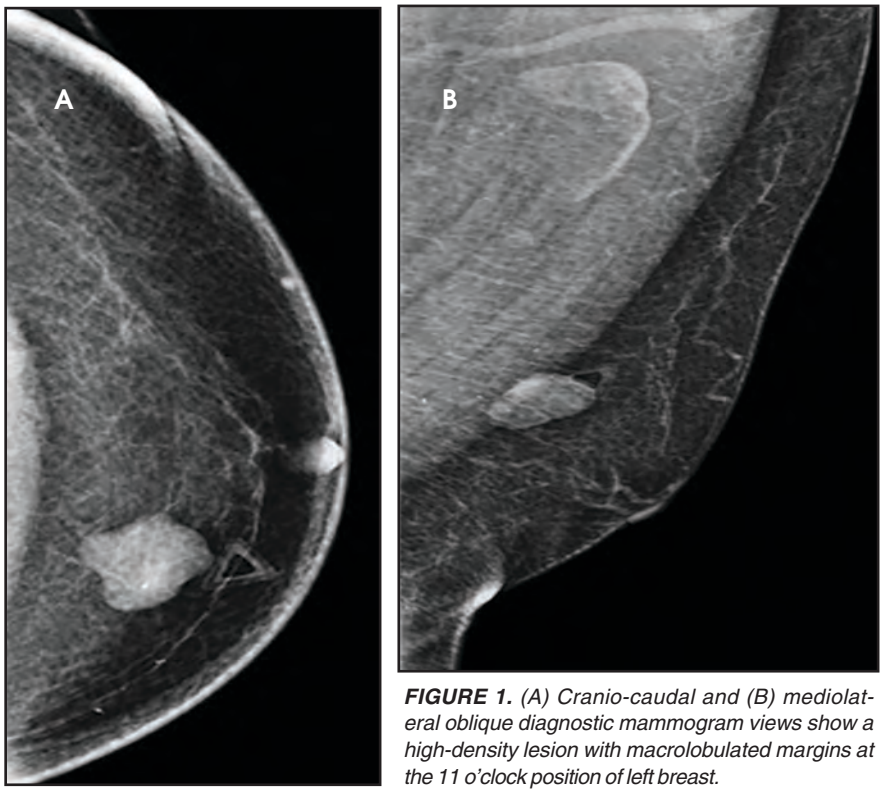

FIGURE 1. *(A) Cranio-caudal and (B) mediolateral oblique diagnostic mammogram views show a high-density lesion with macrolobulated margins at the 11 o'clock position of left breast.*

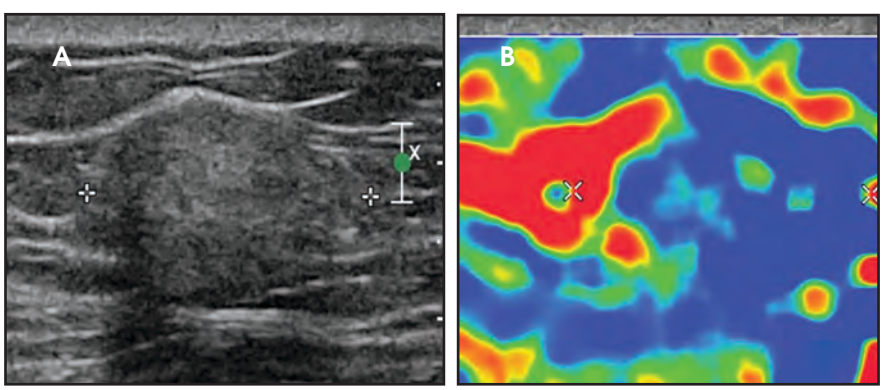

FIGURE 2. *Grayscale ultrasound and elastography (A,B) near the palpable abnormality in the left breast show an elongated, hyperechoic, smoothly marginated mass, parallel to the tissue planes, (calipers). Elastography also reveals hard and soft areas (B).*

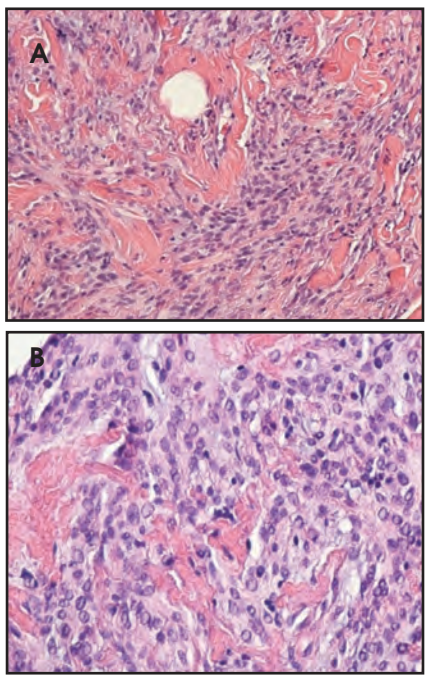

FIGURE 3. *(A) Low-power image shows tumor cells with characteristic spindle cell pattern dispersed among thick bundles of collagen and devoid of breast parenchyma (Hematoxylin and Eosin X 20). (B) High power image showing bland spindle cells with minimal mitotic figures dispersed among collagen bundles (Hematoxylin and Eosin X 40)*

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RADIOLOGICAL CASE

Fibrolamellar Carcinoma

Luz Adriana Escobar, MD; Julian Kirchner, MD; Soleen Ghafoor, MD; Olca Basturk, MD; Richard K Do, MD, PhD

CASE SUMMARY

A 24-year-old presented with left flank pain and urinary symptoms. Unenhanced abdominal CT, performed to exclude nephrolithiasis, revealed an isoattenuating liver lesion with calcifications.

The patient had no previous history of chronic liver disease or alcohol ingestion and the physical examination was unremarkable. Hepatic enzymes were elevated (ALT:1295, AST:1050). Laboratory tests for hepatitis were negative. MRI findings were concerning for fibrolamellar hepatocellular carcinoma (FLC). A CT-guided liver biopsy, followed by surgical resection, confirmed the diagnosis of FLC.

IMAGING FINDINGS

On the unenhanced CT, a few foci of calcification were seen within the scar of the lesion. A CECT obtained for preoperative staging demonstrated a hypervascular liver mass in segment VIII measuring 7 x 6 cm with a nonenhancing central scar (Figure 1). Liver MRI showed a well-defined, lobulated hepatic mass, isointense on T1 images, hyperintense with a hypointense central scar on T2 images, and arterial phase hyperenhancement with a hypoenhancing scar (Figure 2). Pathological analysis of the lesion was performed after resection (Figure 3).

DIAGNOSIS

Fibrolamellar hepatocellular carcinoma (FLC).

Focal Nodular Hyperplasia (FNH) was raised as a diagnostic consideration during review at multidisciplinary tumor board, leading to surgical biopsy before resection.

DISCUSSION

Fibrolamellar hepatocellular carcinoma is an uncommon variant of hepatocellular carcinoma (HCC), with distinct clinical and pathological features and accounting for 1 to 9% of all HCC. Unlike HCC they are not associated with cirrhosis, alcoholism, or hepatitis B/C infection. This tumor occurs more frequently in younger patients (10-31 years of age). Alpha-fetoprotein (AFP) levels are typically normal.[1]

On pathological analysis FLC is characterized by large tumor cells with eosinophilic cytoplasm due to abundant mitochondria and prominent nuclei arranged in cords surrounded by lamellated collagen fibers.[1]

Patients with FLC may be asymptomatic or present with weight loss, fatigue, and/or abdominal pain. At diagnosis more than 80% of tumors present as a large (5 to 20 cm in diameter), well-defined, solid mass with lobulated contours and a central stellate scar. On unenhanced images, small foci of calcifications are seen in 35–68% of cases. After contrast administration, these tumors demonstrate heterogeneous enhancement in the arterial and portal venous phases, with increasing homogeneity on delayed images.[2] The scar is usually non-enhancing and is best visualized on delayed images.

On MRI, FLC appears nearly isointense on T1 images and hyperintense on T2 images, relative to liver parenchyma. The central scar is typically hypointense both on T1 and T2 images. The low signal intensity on T2 imaging and the presence of calcifications distinguish FLC from FNH central scars. After contrast administration, the enhancement pattern is similar to that seen on CT. FLC does not retain hepatobiliary-specific contrast agents, another distinguishing characteristic from FNH. FLC shows restricted diffusion on diffusion-weighted imaging.

Differential diagnoses include FNH, cavernous hemangioma, and hepatocellular carcinoma.[3]

Nodal metastases occur in up to 65% of cases, and distant metastases occur in 20–30% of FLC; common sites are the lungs, peritoneum, and adrenal glands.[4] Resection is the treatment of choice, with a resulting 5-year survival of 76% compared to 37-56% survival for conventional HCC. [5] Recurrence is frequently seen in patients with FLC; thus, post-operative follow-up imaging studies remain important.[1]

CONCLUSION

Fibrolamellar hepatocellular carcinoma is a malignant hepatocellular tumor with demographic, pathological, and clinical characteristics distinct from those of HCC. Knowledge of specific radiological findings on CECT and MRI is important for diagnosing this rare tumor and distinguishing it from the much more common incidental FNH.

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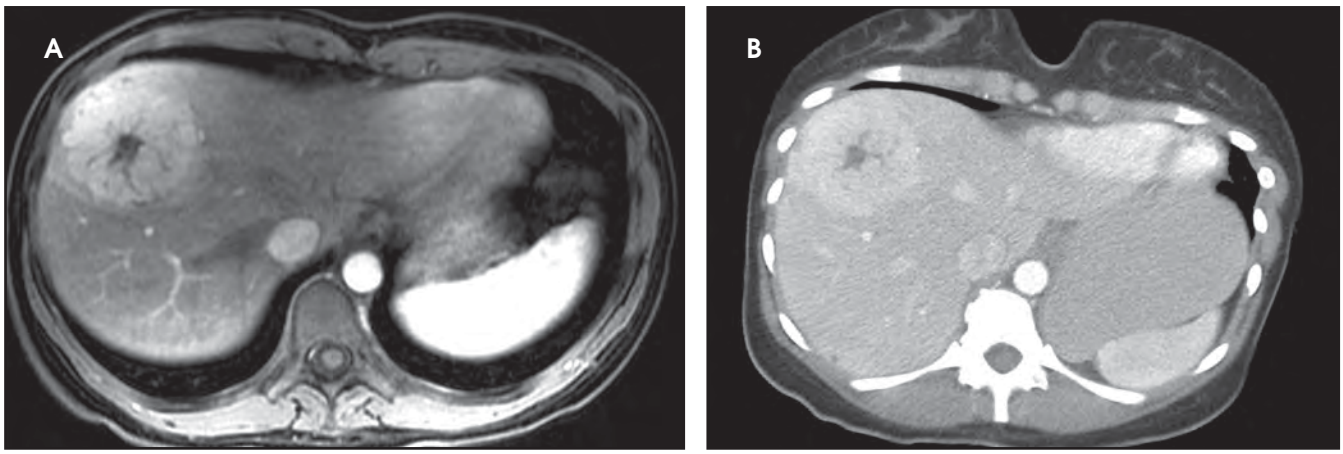

FIGURE 1. *On unenhanced CT (A) a solid mass with few foci of central calcification is seen (white arrow). Contrast-enhanced CT (B) shows a hypervascular, well-defined solid lesion in the right hepatic lobe with a central hypoenhancing scar.*

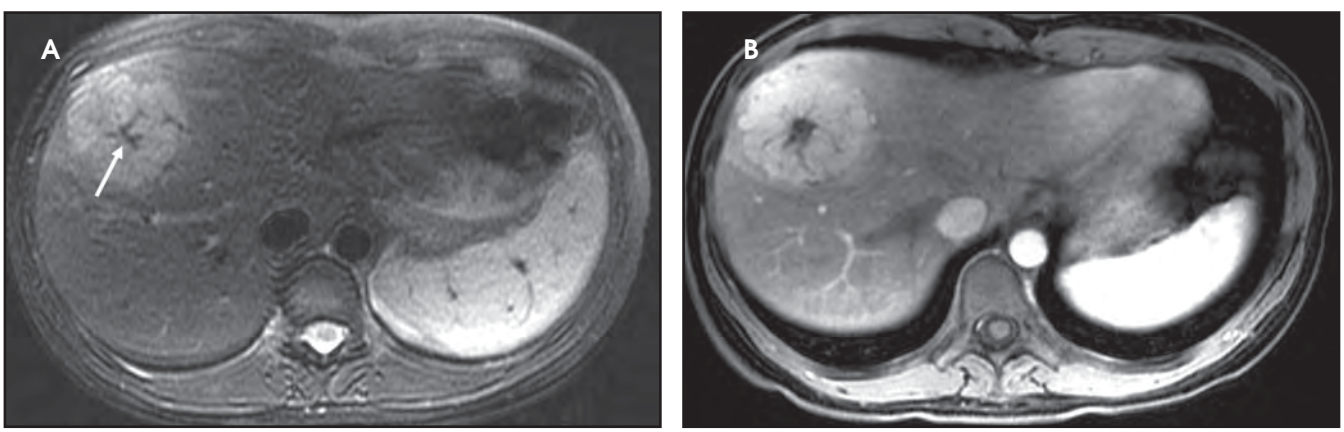

FIGURE 2. *(A) FLC appears hyperintense on T2 MRI image. The central scar and radial septa are hypointense (white arrow). (B) Hypervascular lesion on arterial phase, postcontrast T1 imaging.*

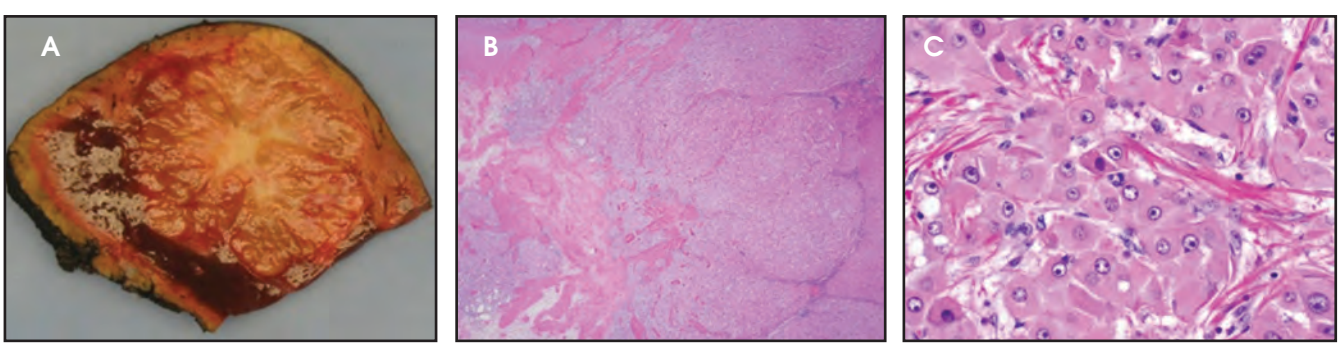

FIGURE 3. *(A) Photograph of the resected specimen reveals a large, relatively well-circumscribed, tan to light brown tumor with central stellate scar. (B) Low- and (C) high-power photomicrographs show sheets or trabecula of large oncocytic cells separated by dense collagen bundles (B) and large polygonal tumor cells with abundant granular and eosinophilic cytoplasm and nuclei.*

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IT (under breath): "How DO these radiologists put their shoes on in the morning? PICNIC."

IT Part Deux: Yes. I Tried Turning it Off.

C Douglas Phillips, MD, FACR

"Idiots emit bogons, causing machinery to malfunction in their presence. System administrators absorb bogons, letting machinery work again."

—Charles Stross, *The Atrocity Archives*

Mr Stross hit the nail on the head. Most of us cause our own IT malfunctions.

Have you heard the term for radiologists who kill IT? PICNIC, meaning "problem in chair, not in computer." Now maybe we didn't know that asking our PACS to pull up an image was wrong, but at that time, it was. And the system rewarded you for asking it to do something it didn't want to do by shutting down.

Here's the scenario:

Your system fails. Something isn't working. You want to dictate, and the system tells you that you don't have a microphone, which is disturbing as you sit there with a microphone in your hand. So, what do you do? Well, I'm pretty sure I know what you do. You turn the damned thing off and back on again.

Reboot. Reboot. Reboot.

Why is it that with computers we have to start using the magic numbers again? I always do everything in threes now, not that it should matter. Some weird superstition.

But it's still not working. Hmm… time to call IT.

Me: "Hi, my workstation isn't working."

IT: "Did you reboot?"

Me: "Of course. Three times."

IT: "What's the tag on the system?"

Me: "The what?"

IT: "The tag. It identifies it. Bottom of the CPU."

Me: Silence.

IT: "You've got to turn it over. Bottom of the CPU."

At this point, I am out of this loop. I didn't sign up for this. I usually feign ignorance, or say, "*No hablo inglés*" over and over. Get someone here to fix it.

And what about the times you've been asked to play computer sleuth, like this:

Me: "Hi, my workstation isn't working."

IT: "Did you reboot?"

Me: "Of course. Three times."

IT: "What do you see on the screen?"

Me: "A small blue box that says, "You have committed the ultimate sin. You must pay penance. Contact the system administrator."

IT: "Okay, what I need you to do is go to the DOS prompt, pull up the sysfile, and then go to the network line, and then—"

Me: "What? I can't type. Why do you think I use voice transcription? What's a DOS prompt? What's a sysfile?"

IT (under breath): "*How DO these radiologists put their shoes on in the morning? PICNIC.*"

IT (audibly): "Okay, we will be there this millennium."

Next month, computerspeak for the non-IT crowd.

Keep doing that good work. Mahalo.

Dr Phillips is a Professor of Radiology, Director of Head and Neck Imaging, at Weill Cornell Medical College, NewYork-Presbyterian Hospital, New York, NY. He is a member of the Applied Radiology *Editorial Advisory Board.*

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RADIOLOGICAL CASE

Inflammatory Pseudotumor of the Nasopharynx

Jay K R Nair, MD; Riaz Shaista, MD; Caglar Derin, MD; Raquel Del Carpio, MD; Jeffrey Chankowsky, MD, CM, FRCPC

CASE SUMMARY

An 87-year-old former smoker presented with severe unrelenting headache following trivial trauma. The patient also had developed recent onset facial numbness and facial palsy. Medical history included hypertension and hypothyroidism, with occasional alcohol ingestion. On examination, patient was cachectic with evidence of muscle wasting but examination was otherwise normal. There was no lymph node enlargement. Nasal examination was suspicious for a left nasopharyngeal mass, which was confirmed by nasopharyngeal endoscopy. Two biopsies of the nasopharyngeal mass demonstrated only fibrous tissue and mild chronic inflammation with no evidence of malignancy.

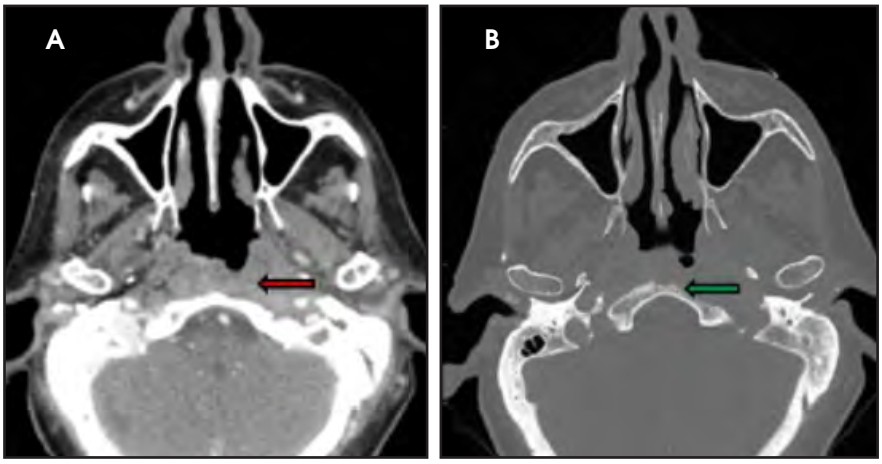

FIGURE 1. *(A) Axial contrast-enhanced CT scan of the nasopharynx demonstrates enhancing nasopharyngeal soft tissue (arrow) predominantly involving the left side. (B) Axial CT bone window shows destruction of the clivus (arrow), extending across the midline.*

IMAGING FINDINGS

Nasopharyngeal inflammatory pseudotumor (IPT) appears as homogeneously enhancing nasopharyngeal soft tissue on contrast-enhanced CT examination. Associated destruction of the skull base (Figure 1) and narrowing of the neighboring skull base foramina/canals may occur. There is usually no enlargement of the cervical lymph nodes.

On MRI, IPTs are typically ill-defined, infiltrative masses (Figure 2) with moderate, homogeneous contrast enhancement. There is involvement of the submucosa of the nasopharynx with preservation of normal hyperintense signal of the nasopharyngeal mucosa. Contiguous structures that may be involved include the clivus, eustachian tube, carotid and parapharyngeal spaces, Meckel cave, orbital apex, and cavernous sinus. Encasement of the internal carotid artery may occur. Ipsilateral opacification of the mastoid air cells is a common finding due to eustachian tube obstruction.

DIAGNOSIS

Inflammatory pseudotumor (IPT) of the nasopharynx.

Differential diagnosis includes nasopharyngeal carcinoma (NPC), chordoma, chondrosarcoma, skull base lymphoma, plasmacytoma, and metastasis. Rosai-Dorfman disease, Epstein-Barr virus-related inflammatory pseudotumor, calcifying fibrous pseudotumor, and sclerosing lymphoma are less likely considerations.

DISCUSSION

Inflammatory pseudotumor (IPT) of the nasopharynx is a benign, idiopathic disease usually mistaken for a neoplasm/infection owing to its aggressive appearance[1,2,3] Patients routinely present with recent history of otitis media, hearing loss, and/or single or multiple cranial nerve neuropathies.[2]

IPT is an inflammatory lesion of unknown etiology. Various theories, including autoimmune reaction linked to viral infection, infectious process due to sinusitis, or syphilis and aberrant production of fibrogenic cytokines, have been proposed.[1] However, recent studies have suggested cytogenetic clonal abnormality and anaplastic lymphoma kinase expression, suspicious for a neoplastic cause.[4]

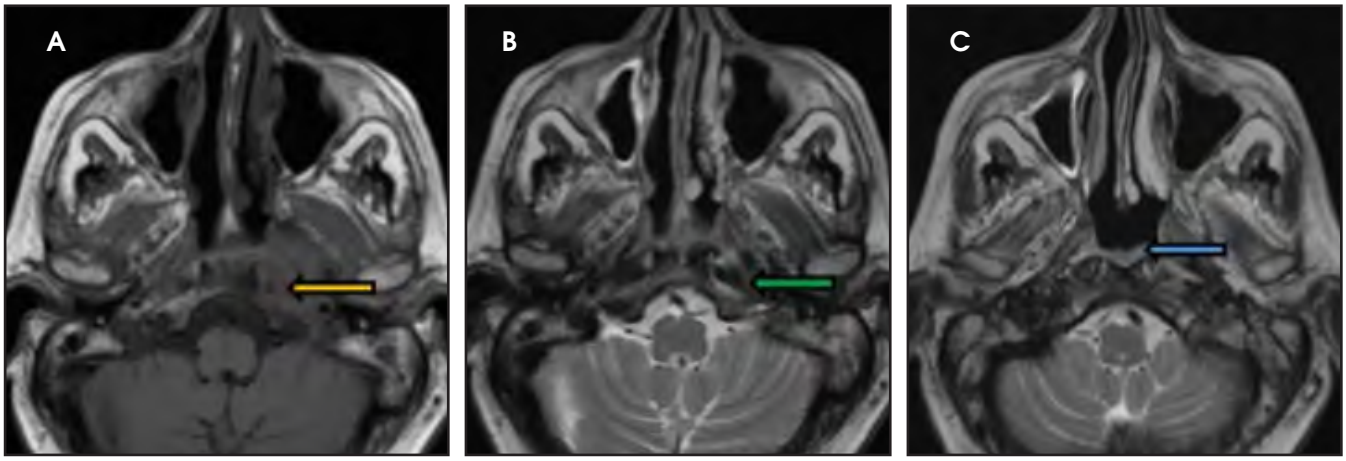

FIGURE 2. *(A) Axial T1 MRI through the nasopharynx shows a soft-tissue mass lesion of the left posterolateral aspect of the nasopharynx (arrow) with destruction of the clivus and left petrous apex. (B) Axial T2 MRI of the nasopharynx demonstrates the low signal in the lesion (arrow). (C) The left nasopharyngeal mucosa (arrow) is unremarkable on axial T2 MRI of the nasopharynx, favoring IPT over NPC.*

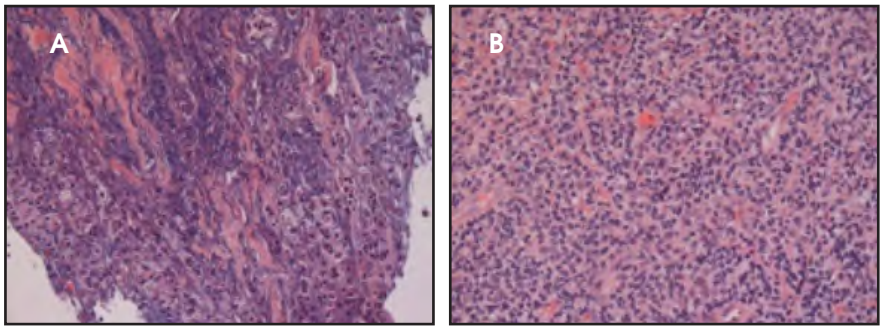

FIGURE 3. *Hematoxylin and eosin stains on microscopy show (A) Neutrophils with areas of necrosis (smudgy purple areas) and fibrous tissue (pink). (B) Lymphocytes (small blue round dark blue cells) are intermingled with plasma cells (slightly larger nuclei with larger pink cytoplasm).*

On gross pathology, IPTs resemble inflamed fibrous tissue with contiguous reactive bone. Routine microscopy demonstrates mixed acute/chronic inflammatory cells and spindle cells with a densely fibrotic background.[5,6] (Figure 3).

On MRI, IPT is typically seen as a mass which is T2 hypointense compared to brain parenchyma (Figure 2), while NPC (the most common differential diagnostic consideration) is more hyperintense on T2 imaging.[1,4] Internal carotid artery encasement and narrowing of the vessel lumen are common features with IPT.[1] In comparison to NPC, IPT involves the submucosal layer of the nasopharynx. The hyperintense mucosal layer is well-delineated from the hypointense submucosal lesion on T2 imaging (Figure 2). Extensive pachymeningeal thickening and enhancement is a more common feature of IPT but not of NPC. Cervical lymphadenopathy is more commonly encountered in patients with NPC than with IPT.[1,2,6] Systemic steroids are the treatment of choice in patients with IPT involving the nasopharynx and skull base.[7]

CONCLUSION

Inflammatory pseudotumor of the nasopharynx is a rare mimicker of nasopharyngeal carcinoma and other neoplastic and infectious lesions involving the skull base.

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RADIOLOGICAL CASE

Intraperitoneal Focal Fat Infarction of the Lesser Omentum

Androniki Kozana, MD; Athina Savva, MD; Konstantinos Psillakis, MD; Maria Kokkinaki MD

CASE SUMMARY

A 56-year-old presented to our emergency department complaining of persistent epigastric pain of 48 hours' duration. The patient had no fever, nausea, vomiting, or diarrhea. The patient's personal and family medical history were unremarkable. On physical examination epigastric rebound tenderness was noted, indicating peritoneal irritation. Blood tests were significant for a normal white blood cell count of 10440/mm^3 (neutrophils 72.2%), a mildly elevated C-reactive protein (CRP) level of 15.42 mg/L, and a mildly elevated serum lactate of 22mg/dl.

IMAGING FINDINGS

Contrast-enhanced CT with oral water-soluble contrast was performed to assess for gastrointestinal perforation and peptic ulcer disease. This was combined with CT angiography (CTA) of the mesenteric vessels to assess for mesenteric ischemia. The CTA was normal (Figure 1). No pneumoperitoneum, ascites, or extraluminal oral contrast were noted. No other CT findings indicative of peptic ulcer disease or gastrointestinal perforation (eg, mucosal discontinuity, hump, foreign body) were observed. No enlarged lymph nodes were evident.

However, a localized, slightly edematous, ovoid, fatty lesion with central radiating, hyperattenuating streaks was detected between the gastric body and the left hepatic lobe. Multiplanar reconstructions confirmed the presence of these fairly circumscribed inflammatory changes, at the expected location of the gastrohepatic ligament (Figure 2).

DIAGNOSIS

Intraperitoneal focal fat infarction of the lesser omentum

DISCUSSION

Intraperitoneal focal fat infarction (IFFI) is a rare condition that may present with acute or subacute abdominal pain.[1] The term was introduced to group numerous entities with focal intraabdominal adipose tissue ischemia and/or necrosis as the common pathogenetic mechanism---torsion of epiploic appendages, infarction of the greater omentum and, rarely, the lesser omentum. They all share similar symptomatology, laboratory findings, and imaging features, and are all associated with a benign prognosis.[2]

Clinical manifestations are often nonspecific, consisting mainly of localized abdominal pain with rebound tenderness, indicating peritoneal irritation. Laboratory tests may reveal mildly raised inflammatory markers (white blood cell count and CRP).[3] In our case, mildly elevated serum lactate was also noted, a finding that prompted CTA.

Related to abdominal pain localization, initial differential diagnoses to consider in a clockwise distribution, include: appendicitis and cholecystitis (right-sided pain), peptic ulcer disease and gastrointestinal perforation

FIGURE 1. *CT angiography of the mesenteric vessels shows no filling defects or significant stenoses of the celiac and superior mesenteric arteries.*

or ischemia (midabdominal area and epigastrium), splenic infarction (left-sided pain), and diverticulitis and pelvic inflammatory disease (left-sided and low abdominal pain).[4,5]

In this setting, CT is the initial modality of choice to exclude acute/surgical pathology requiring urgent treatment and to establish the presence of omental disease.[6] Multiplanar reconstructions are valuable to demonstrate the extent of the process. The imaging protocol may be adjusted to reflect the differential diagnostic considerations,

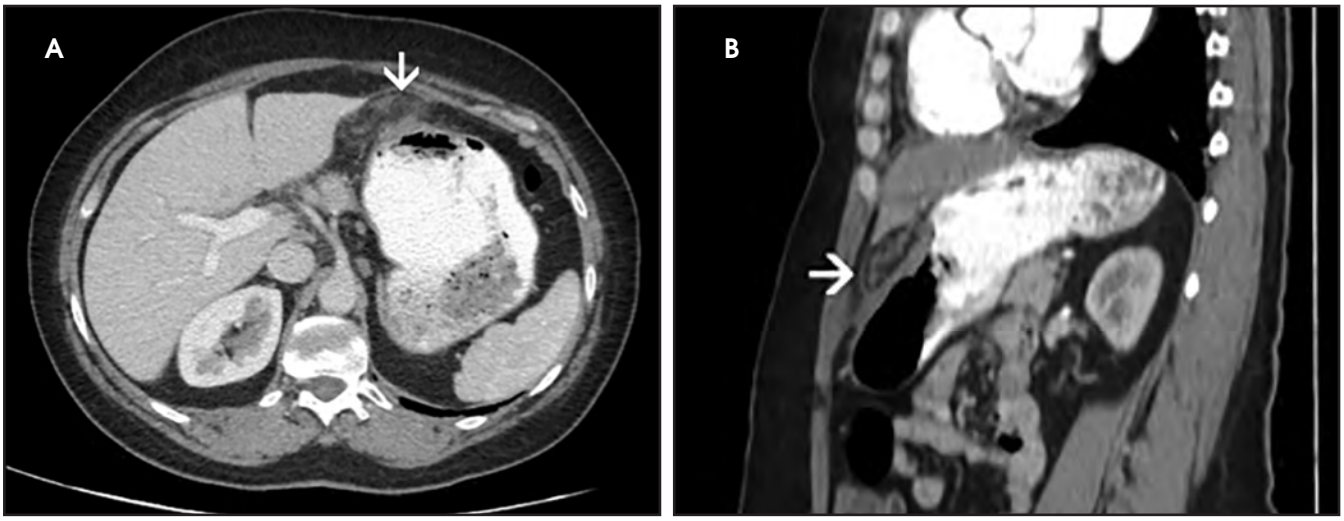

FIGURE 2. *(A) Stranding of the perigastric fat is noted, with minimal mass effect resulting in peritoneal membrane forward bulging. (B) Sagittal reconstruction shows an ovoid fatty lesion at the location of the gastrohepatic ligament.*

including the addition of vascular imaging, as in our case.[7]

The lesser omentum consists of the gastrohepatic and hepatoduodenal ligaments.[8] The former extends from the lesser curvature of the stomach to the inferior surface of the liver, while the latter extends from the proximal duodenum to the porta hepatis. Blood vessels and lymphatics are enveloped within two sheets of peritoneal membrane in a variable amount of adipose tissue.[8] IFFI of the lesser omentum and adipose tissue about the stomach has been referred to as perigastric appendagitis.[9]

CT features indicative of IFFI of the lesser omentum may range from mild stranding of the adipose tissue, to edematous, mass-like changes or swirling haziness around a central vessel, the "whirl" sign, a finding indicative of omental torsion.[8,9] Ultrasonographic changes are usually subtle, mainly consisting of nonspecific echogenic fatty changes and therefore may miss the final diagnosis, given the low awareness of this entity.

Therapeutic management is debatable, owing to the lack of comparative studies and insufficient data. Some advocate exploratory laparotomy and others opt for conservative treatment with analgesics, anti-inflammatory medication, and fluid replacement unless there is a clinical deterioration. Recent literature questions the need for surgery in order to avoid unnecessary cost and perioperative morbidity. Deterioration of symptomatology or laboratory markers warrants surgical exploration.[10]

CONCLUSION

IFFI of the lesser omentum can present with severe epigastric pain mimicking an acute abdomen. Epiploic appendagitis, omental torsion, and omental infarction represent the spectrum of IFFI, share similar pathophysiological etiology, and are rare causes of acute abdominal pain. Watchful waiting is generally considered safe and appropriate. Imaging serves to exclude surgical pathology, to suggest the diagnosis, and to guide management to avoid unnecessary invasive treatment. Radiologists should be aware of this entity and the distinct imaging features consistent with fat inflammation in the distribution of the gastrohepatic and hepatoduodenal ligaments.

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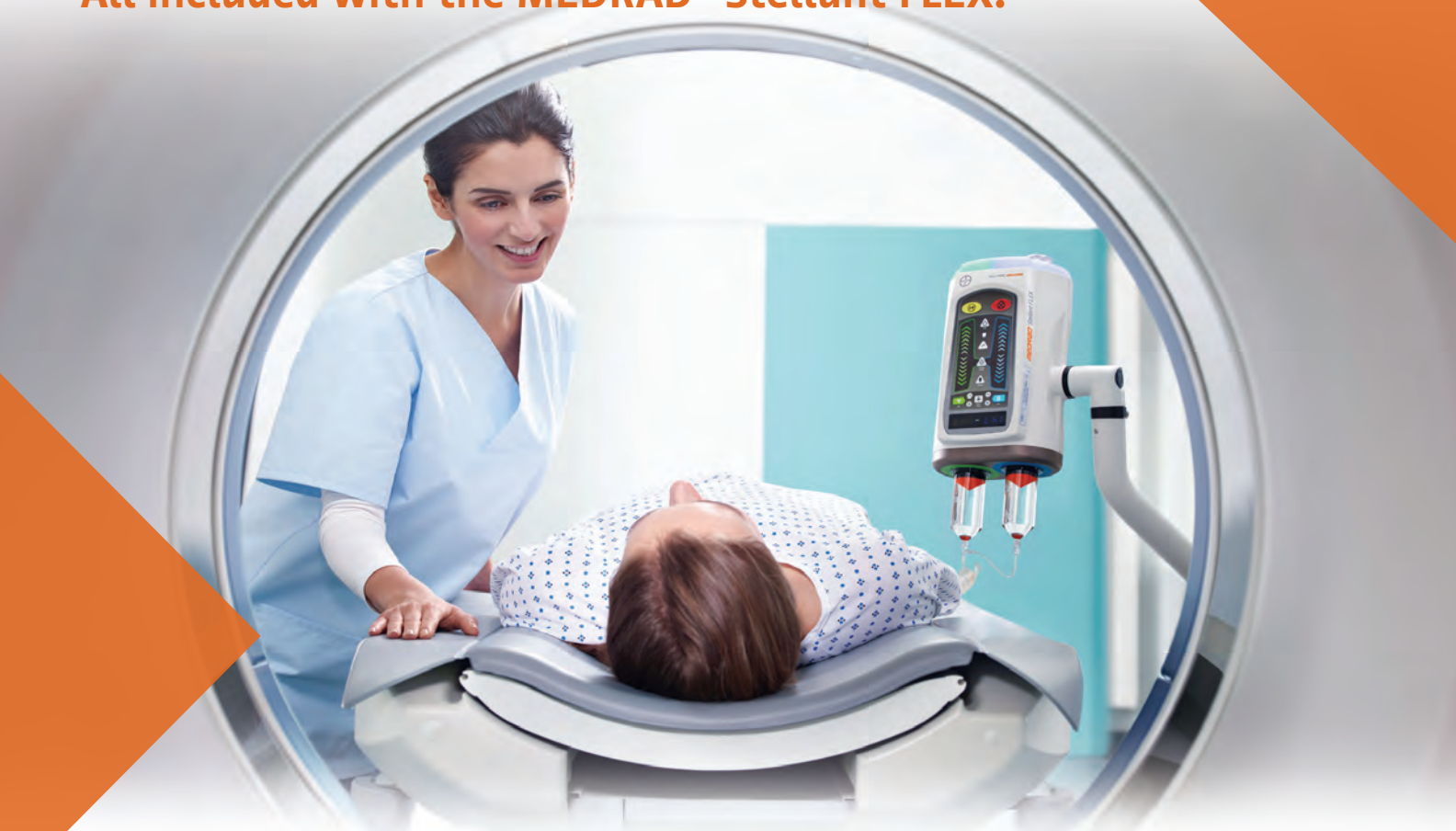

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