Metastatic Neuroblastoma

Amanda L Schaaf; Richard B Towbin, MD; Carrie M. Schaefer, MD; Alexander J. Towbin, MD

Case Summary

A young child presented with a 2-week history of intermittent fever and a 3-day history of a right shoulder mass. They had visited a primary care physician twice in the eight days prior to hospital admission. The first visit occurred eight days prior to admission and was for fussiness, headache, neck pain, fever, right knee pain, and some difficulty ambulating. During this visit, bloodwork showed low hemoglobin (10.8 g/dL), elevated platelets (480 x 10^9/L), and LDH (400 units/L). The second visit occurred one day prior to admission and was for the right shoulder mass.

Imaging Findings

Right shoulder radiographs showed an irregular contour of the right scapula with geographic bone destruction of the scapula and acromion, periosteal new bone formation along the medial scapula and a soft tissue mass projecting superior to the right clavicle (Figure 1). Magnetic resonance imaging (MRI) of the shoulder showed abnormal marrow signal in the right scapula and proximal humerus. In addition, there was a 6.0 cm extraosseous soft tissue mass (Figure 2). Chest CT demonstrated a destructive lesion in the right scapula that correlated with the appearance of the scapula abnormalities on the radiographs and MRI. The bone changes were associated with a large, soft tissue mass along the superior and posterior borders of the scapula (Figure 3). There were also multiple pulmonary masses and a 3.8 cm left-adrenal mass containing multiple calcifications (not shown).

Affiliations: University of Arizona College of Medicine-Phoenix (Ms. Schaaf), Phoenix Children's Hospital (Drs R Towbin, Schaefer); Cincinnati Children's Hospital and Cincinnati College of Medicine (Dr A Towbin).

Histopathological Findings

Percutaneous biopsy of the right scapular mass revealed a poorly differentiated metastatic neuroblastoma with an intermediate mitosis-karyorrhexis index. Concurrent bone marrow biopsy was also positive for metastatic tumor.

Diagnosis

Metastatic neuroblastoma.

The differential diagnosis includes Ewing sarcoma, lymphoma, and undifferentiated soft-tissue sarcomas such as rhabdomyosarcoma.

Discussion

Neuroblastoma is a tumor of neural crest origin.[1] Although rare, neuroblastoma accounts for 7% of cancers and 15% of cancer death in children.[2] It is the most frequently diagnosed solid tumor in children with 95% of all diagnoses made before five years of age.[1] The early age at diagnosis suggests that prenatal factors may play a role in tumor development.[1] Several studies have identified potential parental risk factors associated with development of neuroblastoma in offspring. These potential risks include maternal alcohol consumption and/or tobacco use during pregnancy; parental occupations that include exposures to electromagnetic fields, pesticides, or hydrocarbons; and certain medications taken during pregnancy such as oral contraceptives, hormones, diuretics, or codeine.[1]

Several types of gene expression and chromosomal abnormalities have been found to play a role in the emergence of and pathogenesis of neuroblastoma.[1] The MYCN oncogene is perhaps the most important chromosomal risk factor. It is amplified in at least 20% of patients with neuroblastoma. MYCN amplification is more common in patients with Stage 4 disease and is correlated with more rapid tumor growth and worse survival rates.[3] Other genes involved in neuroblastomas are TRK, CD44, and ALK.

Neuroblastoma can occur anywhere along the sympathetic nervous system from neck to pelvis. However, 65% of tumors are abdom-

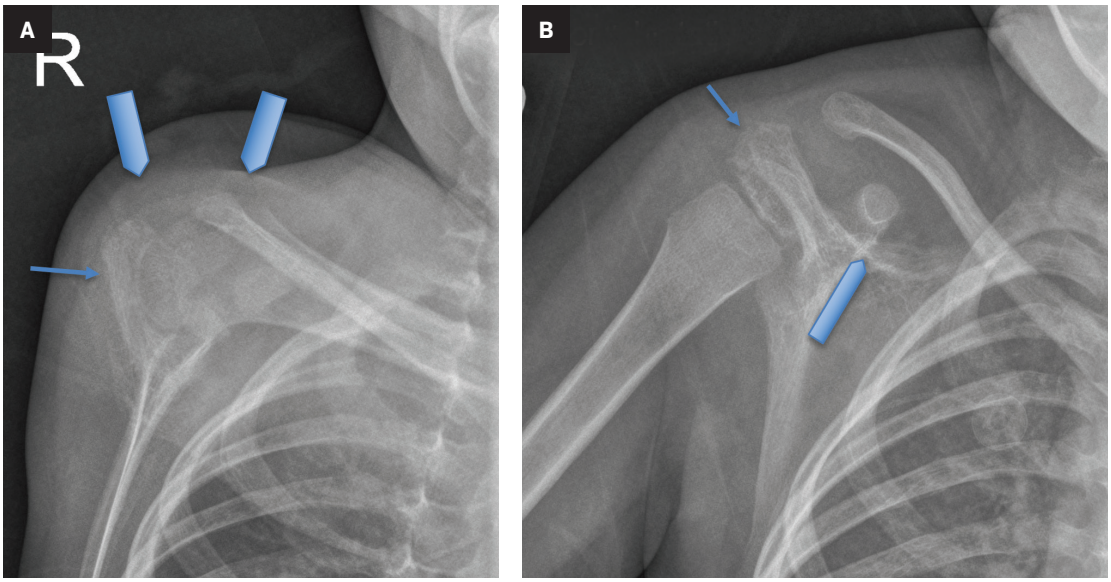


Figure 1. (A) Y-view of the right scapula shows an irregular contour of the medial aspect of the right scapula with a moth-eaten destruction (thin arrow) of the acromion and superior scapula. A soft-tissue mass (thick arrows) projects superior to the right clavicle. (B) External rotation radiograph shows a soft-tissue mass (thick arrow) and destruction (thin arrow) of the superior scapula and acromion process.

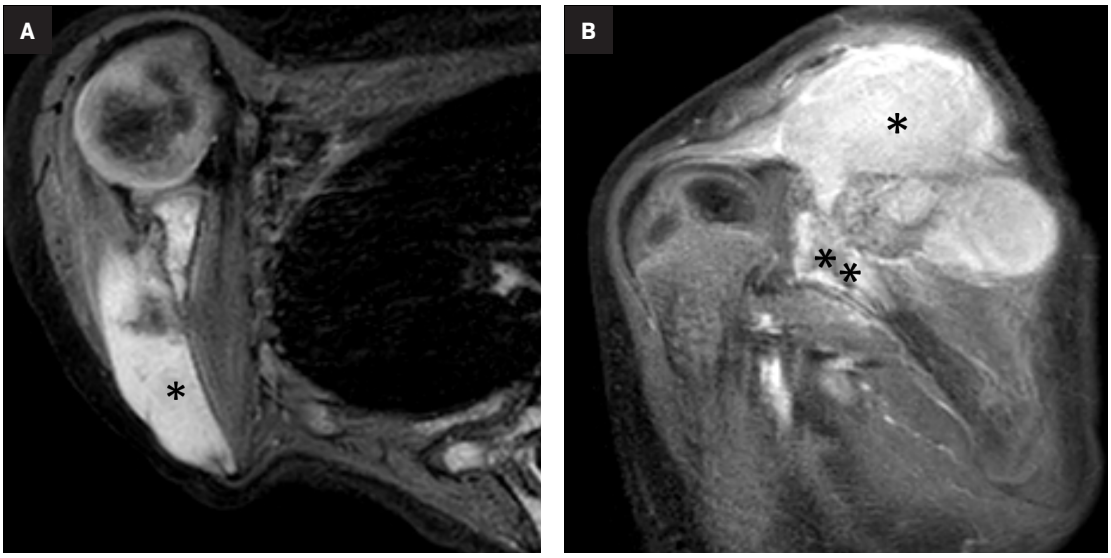


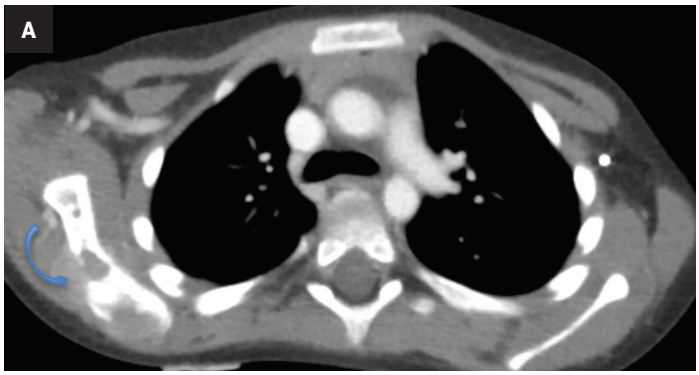
Figure 2. MR imaging of the right shoulder shows T1 hypointensity (A) and T2 hyperintensity (B) of the right scapula, as well as mottled T1 hypointensity and T2 hyperintensity of the proximal humeral shaft. Bone marrow replacement (**) in the right scapular was also observed, with a 6.0 x 5.9 x 3.2 cm extraosseous soft-tissue mass (*). Given the adrenal mass, metastatic neuroblastoma was a favored diagnosis.

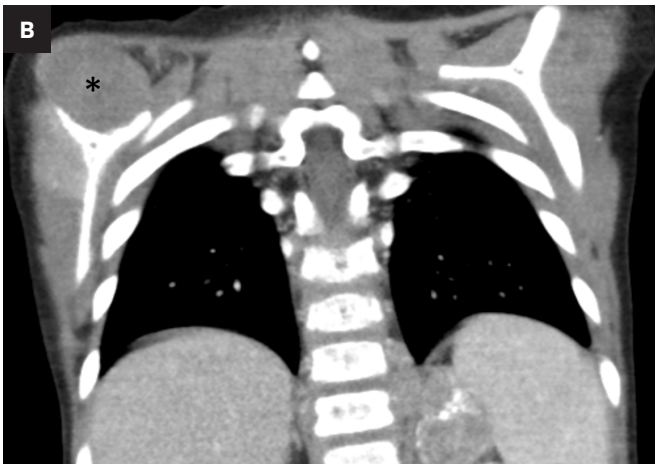
inal and 46% arise from the adrenal gland. Symptoms depend on size and location of the mass. Most patients present with a palpable abdominal mass and/or abdominal distension.[3,4] Children may have symptoms related to constipation or hypertension.[3] Tumors present in the chest may cause scoliosis or airway compression.[3] Paraspinal tumors that invade the spinal canal can cause neurological symptoms and signs such as pain, motor or sensory deficits, and Horner syndrome.[3] Although rare, pulmonary metastases may occur.[5]

Metastases occur in 40% of patients.[1] Bone and bone marrow are the most frequent sites of metastasis; bone marrow represents as much as 70% of metastatic sites in patients.[1,2,4] Other common metastatic sites include the liver and regional lymph nodes.[4] The majority of metastatic neuroblastoma patients present with systemic symptoms like fever, pain, and weight loss.[3]

Imaging plays a role in identifying metastatic disease. Skeletal metastases are often first identified via I-123 metaiodobenzylguanidine (MIBG) scintigraphy. Normally, there is no uptake of the radiotracer in bone. Therefore, bones visible on the planar images of an MIBG scan confirm the presence of metastatic disease. Occasionally, children present with other bone-related symptoms, such as a limp. Radiographs obtained for this indication may show lucent metaphyseal bands, geographic lucency, or a permeative appearance of the bone. Skull metastases may cause thickening and a periosteal reaction. Because bone metastases cannot be distinguished from marrow metastases, a bone marrow biopsy is part of the standard work-up in newly diagnosed cases of neuroblastoma.

MRI is commonly used to evaluate the primary tumor, to identify image-defined risk factors, and to





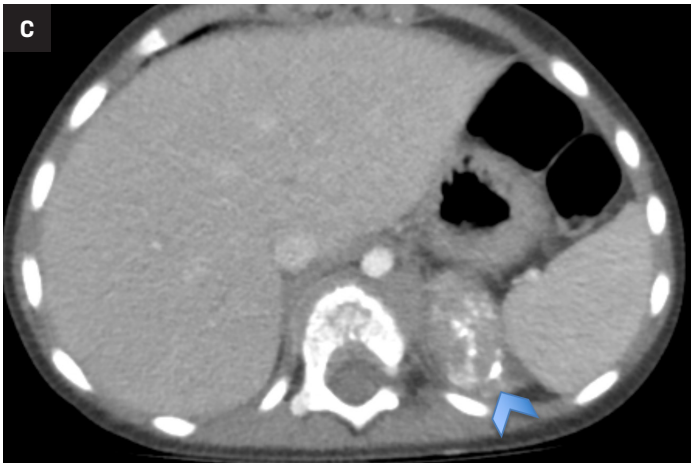


Figure 3. Axial CT of the chest (A) revealed a large destructive lesion in the right scapula, causing a moth-eaten appearance of the bone (curved arrow). (B) Coronal CT shows a large, soft-tissue mass (*) along the superior and posterior borders of the scapula. In addition, an oval-shaped soft-tissue lesion (chevron) with calcifications is present in the left suprarenal region.

determine local-regional spread of disease. While MRI can help to identify bone metastases, it is not often the primary modality for this purpose. This is because of the potential for widespread disease and the fact that bone changes lag behind functional changes. Consequently, MIBG, which allows for whole-body imaging and evaluates the functional nature of the tumor, is the preferred modality for diagnosis and follow-up of metastatic disease.

The prognosis for patients diagnosed with neuroblastoma depends on age at diagnosis, extent of disease, presence of image defined risk factors, tumor differentiations, MYCN amplification, and other chromosomal abnormalities. Patients with metastatic neuroblastoma can be stratified into low-, intermediate-, or high-risk groups.[6] Studies suggest that for low- and intermediate-risk patients, complete resection of the tumor is often unnecessary for recovery.[3] Patients of intermediate risk may receive chemotherapy to shrink their tumor before undergoing surgery.[3] For high-risk patients, treatment includes neoadjuvant chemotherapy, surgical resection, adjuvant high-dose chemotherapy, with hematopoietic stem cell rescue, and radiation therapy.[3] Low-risk patients have a 5-year event-free survival rate of 75-85%. This rate falls to 50-75% for patients with intermediate risk and less than 50% for children with high-risk disease.

Conclusion

Despite the rarity of neuroblastoma, it accounts for up to 15% of pediatric cancer fatalities.[3] Bone and bone marrow are two of the most common sites of metastasis.[3] The highly variable symptoms of neuroblastoma make diagnosis challenging, especially in patients with atypical symptoms. Although uncommon, neuroblastoma should be considered in the differential diagnosis of patients presenting with bone pain and protean systemic symptoms like fever.

References

1) Luksch R, Castellani MR, Collini P, et al. Neuroblastoma (Peripheral neuroblastic tumours). *Crit Rev Oncol Hematol.* 2016;107:163–181.

2) Chu CM, Rasalkar DD, Hu YJ et al. Clinical presentations and imaging findings of neuroblastoma beyond abdominal mass and a review of imaging algorithm. *Br J Radiol.* 2011; 84:81–91.

3) Swift CC, Eklund MJ, Kraveka JM, Alazraki AL. Updates in diagnosis, management, and treatment of neuroblastoma. *Radiographics.* 2018; 38:566–580. doi: 10.1148/rg.2018170132.

4) David R, Lamki N, Fan S, et al. The many faces of neuroblastoma. *Radiographics.* 1989; 9(5):859-882. doi:10.1148/radiographics.9.5.2678295.

5) Towbin R, Gruppo R: Pulmonary metastases in neuroblastoma. *Am J Roentgenol.* 1982; 138:75-78.

6) Cohn SL, Pearson AD, London WB, et al. The International Neuroblastoma Risk Group (INRG) Classification System: An INRG Task Force Report. *J. Clin. Oncol.* 2009;27:289–297. doi: 10.1200/JCO.2008.16.6785.