Multifocal Intraosseous Ganglioneuroma

Daniel G. Kang, MD, Melvin D. Helgeson, MD, Jennifer D. Britt, DMD, Robert W. Tracey, MD, and Joshua D. Bernstock, MS, MPH

Abstract

We report a case of asymptomatic intraosseous ganglioneuroma of the ilium, which was initially misdiagnosed as polyostotic fibrous dysplasia. Our patient presented with multiple asymptomatic skeletal lesions. Despite extensive work-up of our patient to rule out metastatic disease, we were unable to find a primary source; biopsy showed intraosseous ganglioneuroma of the ilium. To the best of our knowledge, we report an exceedingly rare pathologic entity; only 3 cases have been described of intraosseous ganglioneuroma from spontaneous cytomaturation of metastatic neuroblastoma.

Knowledge of the natural history of ganglioneuroma is limited, but patients with primary and multifocal disease appear to have benign histologic tumor appearance and excellent prognoses. Similar to previous studies, the rarity of this tumor and its nonspecific radiographic and clinical presentation resulted in the correct diagnosis only after histopathologic analysis. Because intraosseous ganglioneuroma may mimic fibrous dysplasia it should be considered in the differential diagnosis of benign-appearing skeletal lesions, particularly if the patient has a history of neuroblastoma.

Ganglioneuromas are rare, enigmatic tumors considered to be the benign subset of neuroblastic tumors.[1,2] An extensive review of the literature revealed only 3 case reports of intraosseous ganglioneuroma developing from spontaneous differentiation of metastatic neuroblastoma.[3-5] We report a case of asymptomatic intraosseous ganglioneuroma of the ilium, which was initially misdiagnosed as polyostotic fibrous dysplasia. The patient provided written informed consent for print and electronic publication of this case report

Case Report

A 51-year-old man was initially evaluated for persistent headaches by the neurology service, and magnetic resonance imaging (MRI) of the brain showed an unusual expansile lesion in the clivus with low T1-signal and high T2-signal intensity (**Figure 1A**). Computed tomography (CT) imaging of the head showed a "ground-glass" appearance consistent with fibrous dysplasia rather than hemangioma (**Figure 1B**). A skeletal survey showed mixed lytic-sclerotic lesions (central lucency with peripheral margin of sclerosis) in the right ilium just above the acetabulum (4.5 × 5.2 cm) and a smaller lesion in the left ilium (1.1 × 1.8 cm; **Figure 2**). Additionally, lytic, well-defined lesions were identified in the distal left humerus (4.1 × 2.0 cm),

Figure 1. (A) Sagittal T2-weighted magnetic resonance imaging of brain and (B) computed tomography of head show expansile lesion in clivus.

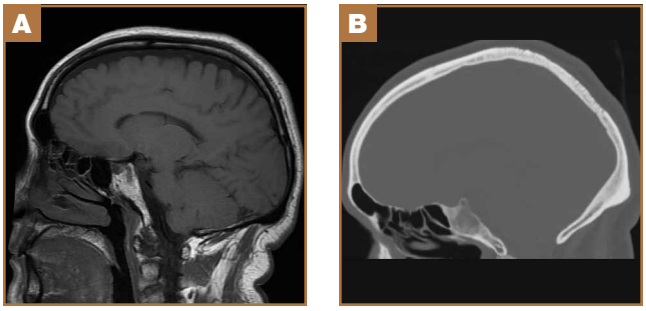
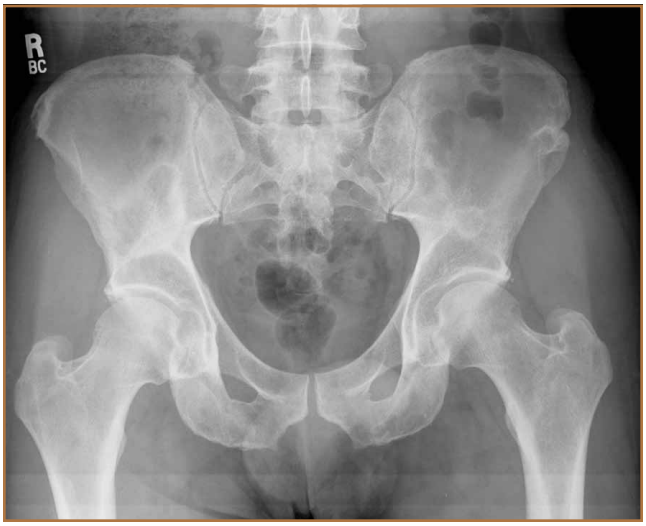


Figure 2. Plain anteroposterior radiograph of pelvis show lytic lesions with sclerotic margins.



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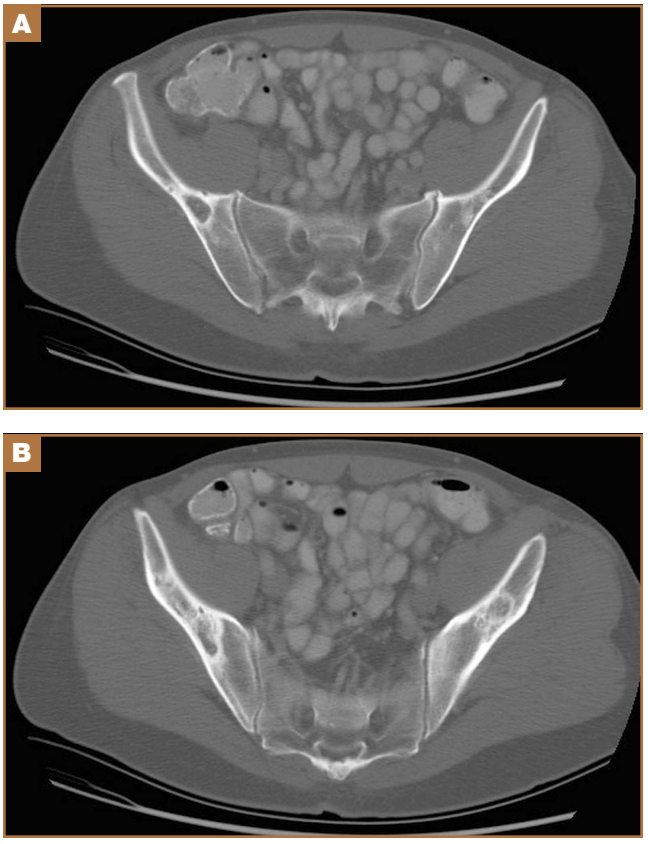

Figure 3. (A, B) Axial computed tomography images of pelvis.

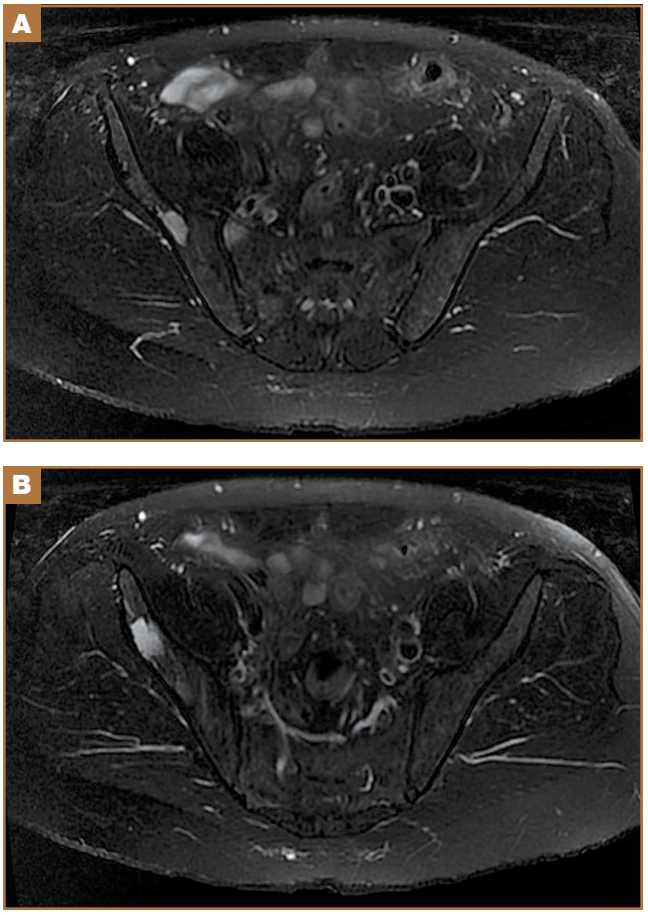

Figure 4. (A, B) Axial T2-weighted magnetic resonance imaging of pelvis.

left proximal femoral diaphysis (5.6 × 1.1 cm), and left proximal tibia diaphysis (10.0 × 1.5 cm). These multiple skeletal lesions were asymptomatic, and based on characteristic radiographic findings, the patient was diagnosed with polyostotic fibrous dysplasia; treatment consisted of observation.

The patient was referred to the orthopedic oncology clinic 3 years, 5 months after initial presentation for evaluation and skeletal lesion biopsy because of concern for metastatic disease of unknown origin. The patient reported that a neuroblastoma tumor was removed from his mediastinum at 10 years of age, with no chemotherapy or radiation therapy. Attempts to retrieve his 1960s medical record and a query of the Armed Forces Institute of Pathology (AFIP) for an archived tissue sample/report were unsuccessful. On physical examination, the patient appeared cachectic because of a recent involuntary 50-pound weight loss; however, the remainder of his musculoskeletal and neurologic examination was unremarkable. Laboratory studies also showed normal findings, which included a complete blood cell count with differential analysis, liver function tests, alkaline phosphatase, basic metabolic panel (electrolytes, renal function tests), erythrocyte sedimentation rate, thyroid function tests, parathyroid hormone level, prostate serum antigen, and lactate dehydrogenase level.

A metastatic disease work-up, which included chest/abdomen/pelvis (C/A/P) CT imaging with contrast, did not show a primary source of disease. The skeletal lesions were further characterized on the C/A/P CT images, and MRI of the pelvis showed multiple mixed lytic and sclerotic lesions in the pelvis (CT: "ground-glass" appearance; MRI: low signal intensity on T1-weighted images and high signal intensity on T2-weighted images), expansile-elongated lesions of the right fifth and sixth posterior ribs, and multiple sclerotic densities throughout the lower thoracic and lumbar spine (**Figures 3 and 4**). Technetium-99m scintigraphy showed a subtle focus of mildly increased tracer activity in the right supra-acetabular ilium, along with multiple other areas of increased activity that could indicate metastatic disease, such as the proximal right femur, mid-left femoral diaphysis, proximal left tibia diaphysis, and bilateral scapulae (**Figure 5**).

Although radiographic findings suggested polyostotic fibrous dysplasia (irregularly defined, hazy radiolucency with a zone of reactive sclerosis and involvement of the ribs),[3,6] the uncertainty of metastatic disease of unknown origin and the patient's clinical presentation warranted biopsy. Initially, we attempted CT-guided percutaneous needle biopsy of the right ilium lesion; this was unsuccessful because of inadequate tissue sampling. Subsequently, we performed an intralesional biopsy of the right ilium (periacetabular) lesion, which showed ganglioneuroma, and AFIP review confirmed it. The hema-

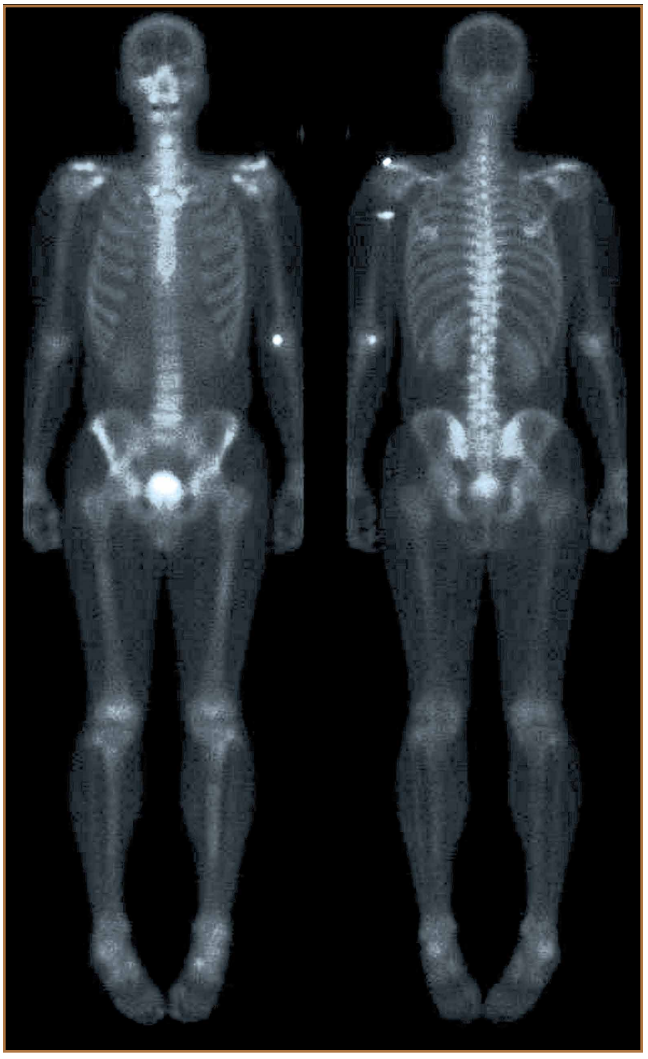

Figure 5. Technetium-99m bone scan with multiple areas of increased tracer activity.

toxylin-eosin–stained surgical specimen showed a neoplasm composed of bland "wavy" spindle cells admixed with large epithelioid ganglion cells. Fragments of vital cortical bone were identified within the loose, variably myxoid, fibrous connective tissue stroma (**Figures 6A, 6B**). The neoplastic cells were strongly immunoreactive for S-100 protein (**Figure 7**). We did not identify any malignant features, and the histopathologic features supported interpretation as ganglioneuroma.

At 5-year follow-up, the patient remains asymptomatic without interval radiographic changes to the skeletal lesions. The patient reports his weight has remained stable since his initial presentation, and the reported involuntary weight loss 5 years ago has been attributed to a diagnosis of polymyalgia rheumatica.

Discussion

Neuroblastic tumors include neuroblastoma, ganglioneuroblastoma, and ganglioneuroma, with each derived from primordial neural crest cells that form the sympathetic nervous system.[2] However, each is of varying maturity and malignancy potential, ranging from neuroblastoma, which is the most immature, undifferentiated, and malignant tumor, to benign ganglioneuroma, which is composed entirely of gangliocytes and mature Schwannian stroma, without neuroblasts, cellular atypia, mitotic activity, or necrosis.[2,3] Neuroblastoma is the most common extracranial malignant solid tumor of childhood, found most frequently in the posterior mediastinum, retroperitoneum, adrenal gland, and neck, and is often diagnosed during the first 3 years of life.[2,4] Bone is the most common site of metastasis, present in up to two-thirds of patients at the time of diagnosis, and is associated with a low rate of survival.[2,3,7]

In 1927, Cushing and Wolbach[8] described the phenomena of clinical regression and histologic maturation of a neuroblastoma to ganglioneuroma.[8] Controversy continues regarding the natural history of neuroblastoma, and the prevalence of

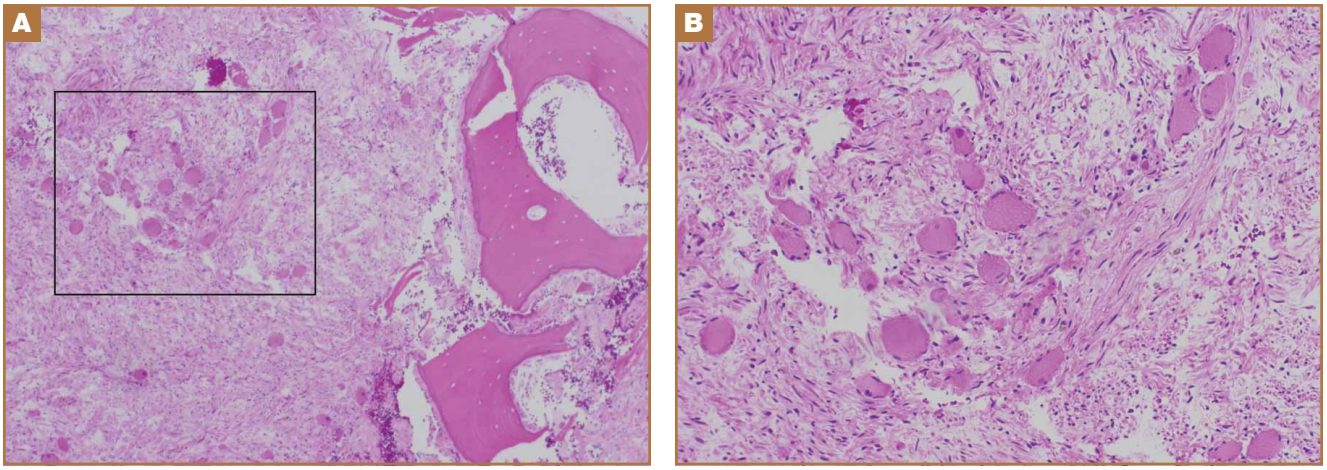

Figure 6. Excisional biopsy from the left ilium shows a neoplasm composed of bland "wavy" spindle cells admixed with large epithelioid ganglion cells. Fragments of vital cortical bone are identified within the loose, variably myxoid, fibrous connective tissue stroma. (A) hematoxylin-eosin (H&E), original magnification ×4; (B) H&E, original magnification ×20.

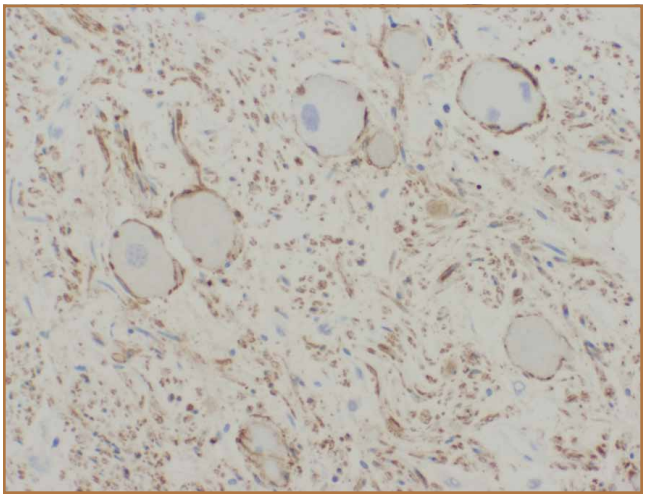

Figure 7. Neoplastic Schwann cells and ganglion cells show strong immunoreactivity for S-100 protein (original magnification ×20).

cytomaturation of neuroblastoma to ganglioneuroma remains unknown, although some believe this occurs in 1% to 2% of neuroblastomas.[2,9,10] Several authors conjecture that apoptosis is possible in every neuroblastic tumor, but some may be inactivated spontaneously by genetic factors, or possibly after chemotherapy or radiation therapy.[1,11,12] In fact, cytomaturation to ganglioneuroma has also been documented in 2 cases of metastatic intraosseous neuroblastoma treated with chemotherapy and radiation therapy.[1,13,14] Garvin and colleagues[4] suggested maturation may also depend on host environmental factors, particularly nerve growth factor, which is essential for differentiation and maintenance of sympathetic neurons. However, in a study by Sonnenfeld and Ishii,[15] nerve growth factor was administered at high levels to undifferentiated neuroblastoma cell lines in vitro and showed partial cytodifferentiation, but, unexpectedly, neither reduced the growth rate nor enhanced survival in any neuroblastoma cell line. Spontaneous differentiation should be distinguished from treatment-related (chemotherapy or radiation) differentiation, because patients with spontaneous maturation are believed to have excellent prognoses, whereas the latter group does not.[3,16,17] Also, when osseous involvement is identified, the presence of a soft-tissue ganglioneuroma with secondary erosion into bone should be distinguished.[3,5]

Our patient presented with multiple asymptomatic skeletal lesions, initially diagnosed as polyostotic fibrous dysplasia; however, biopsy showed intraosseous ganglioneuroma of the ilium. Despite extensive work-up of our patient, we were unable to find another primary source for metastatic disease. To the best of our knowledge, we report an exceedingly rare pathologic entity, with only 3 previous cases described of intraosseous ganglioneuroma from spontaneous cytomaturation of metastatic neuroblastoma.[3-5] Clinicians have postulated that intraosseous ganglioneuroma begins with disseminated neuroblastoma and results when necrosis or apoptosis of immature neuroblasts in metastatic lesions leaves behind the mature ganglion cells and stroma, which had coexisted with the neuroblasts.[1,2] This theory is further supported by the fact that skeletal metastases of neuroblastoma appear to be polyostotic with a predilection for long bones and spine. These were the predominant sites in our patient, as in all 3 previously reported cases of disseminated skeletal ganglioneuroma.[3,13]

Our patient's history of a mediastinal neuroblastoma tumor as a child treated with excisional biopsy without chemotherapy or radiation therapy leads us to believe that spontaneous cytomaturation of metastatic neuroblastoma is the most likely explanation for the occurrence of intraosseous ganglioneuroma. Despite other explanations, the concept of metastasizing benign ganglioneuroma is untenable because mature ganglion cells have no capacity for migration or proliferation,[1,2] and primary osseous ganglioneuroma does not occur, although there has been a report of a primary intraosseous malignant peripheral nerve sheath tumor.[18] Although 1% of patients with disseminated neuroblastoma may have no discoverable primary tumor,[2] if a primary neuroblastoma tumor is identified, excisional biopsy is considered mandatory to identify and remove any remaining malignant potential.[3]

Knowledge concerning the natural history of ganglioneuroma is not extensive, but patients with primary and multifocal disease appear to have benign histologic tumor appearance and excellent prognoses.[2] However, there have been a few case reports of ganglioneuroma spontaneously transforming to a malignant peripheral nerve sheath tumor or of neuroblastoma that has undergone cytomaturation to ganglioneuroma with subsequent recurrent neuroblastoma many years later.[19-25] Despite the rare report of malignant conversion, Mithöfer and colleagues[3] suggested that the differentiation, maturity, and slow-growing behavior of intraosseous ganglioneuroma afford no role for radiation or chemotherapy.[26] Indications for operative treatment include incapacitating pain, potential for fracture, or progressive deformity for involved long bones and vertebrae.

As in previous studies, the rarity of this tumor and its nonspecific radiographic and clinical presentation resulted in the correct diagnosis only after histopathologic analysis. Therefore, intraosseous ganglioneuroma may mimic fibrous dysplasia and should be considered in the differential diagnosis of benign-appearing skeletal lesions, particularly if the patient has a history of neuroblastoma. Also, repeat radiographs should be performed in the presence of new symptoms or pain, and biopsy should be considered if there is progressive disease or changes in skeletal lesions.

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