Giant Cell Reparative Granuloma of the Small Bones of the Hands and Feet: a Report of Three Cases

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Abstract. Giant cell reparative granuloma (GCRG) involving the small tubular bones of the hands and feet is a rare entity that can have a wide range of morphologic presentations and can be confused with more aggressive tumors. Awareness of this lesion is important to avoid diagnostic errors and potential mismanagement. We report three cases of GCRG that involve the small tubular bones of the hands and feet, with long-term follow-up periods that confirm a benign course. Previous reports included the differential diagnosis of giant cell tumor, brown tumor of hyperparathyroidism, aneurysmal bone cyst, and non-ossifying fibroma. The presence of chondroid material in two of our cases, one of which also shows atypical nuclei and a periosteal reaction, expands the differential diagnosis to include bone- and cartilage-forming neoplasms.

Keywords: Giant cell reparative granuloma, bone lesions, pediatric tumors

Introduction

Giant cell reparative granuloma (GCRG), a lesion of uncertain etiology, is thought to be reactive and not neoplastic, even though 30 to 50% of primary lesions recur [1-3]. GCRG typically involves the skull and jaw. Similar lesions in vertebrae are described using the term "solid variant of aneurysmal bone cyst." In a broad sense, any reactive bone lesion with a fibrous stroma that contains a significant number of giant cells can be described as a giant cell reparative granuloma or a giant cell reaction. The typical radiographic appearance is an expansile, multilocular, cystic lesion with an intact cortex. Histologically, the lesion shows a variably cellular fibroblastic stroma with intermixed giant cells. Mitotic figures and osteoid may be present, and evidence of hemorrhage often exists. The differential diagnosis reported in the literature includes giant cell tumor, brown tumor of hyperparathyroidism, aneurysmal bone cyst, and non-ossifying fibroma [1-7].

Case reports

Case 1. A 15-year-old girl presented with the complaint of pain in her right foot for 1.5 mo. The patient first noticed the pain after dropping an object on her foot and subsequently experienced pain on movement and weight-bearing. Physical examination revealed pain upon palpation of the dorsum of her right foot. There was no ecchymosis and the pulses were full. Sensation was intact and there was full range of motion of ankle and toe joints. Pertinent laboratory findings included normal concentrations of serum calcium and phosphorus. X-ray examination showed a lytic lesion in the distal third metatarsal of the right foot with erosion of the cortex and periosteal reaction (Fig. 1).
Giant cell reparative granuloma

Fig. 1. Sharply circumscribed, expansile, multiloculated, radiolucent, cystic lesion of the metatarsal, with erosion of the cortex and periosteal reaction around the areas of cortical destruction. This raised a question of malignancy during radiographic interpretation.

Fig. 2. Osteoid and bone formation surrounded by osteoblasts and osteoclasts (decalcified, H&E, x100).

A fractured metatarsal bone was noted during surgery and an open biopsy was performed. The frozen section revealed significant new bone formation that raised the question of osteosarcoma versus giant cell tumor with osteoid formation. Amputation of the metatarsal was performed. Permanent sections revealed a variable cellular stroma. The cells included numerous giant cells, histiocytes, fibroblasts, and inflammatory cells. Foci of osteoid and chondroid formation, occasionally surrounded by atypical nuclei, were prominent throughout the lesion (Figs. 2, 3). Erosion of the cortex associated with periosteal reaction was noted (Fig. 4). This was thought to be the cause of the fracture. Hemosiderin and phagocytic histiocytes were present throughout the lesion, in particular beneath the eroded cortical bone.

An initial diagnosis of GCRG was made and the case was referred for consultation. In the differential diagnosis, brown tumor of hyperparathyroidism, chondroblastoma, and GCRG with metaplastic
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Fig. 4. GCRG (black arrow) with erosion of the cortex and associated periosteal reaction (asterisk). There is new osteoid to the upper right of asterisk. Normal cortical bone is also present (white arrow) (H&E, x100).

Fig. 5. Radiograph shows a sharply circumscribed, expansile, multiloculated, radiolucent lesion in the proximal phalanx of the thumb.

chondroid were considered. Recurrences have not occurred during 17 years of follow-up.

Case 2. A 12-year-old girl presented with a painful swelling of her right thumb of 2 mo duration. She reported minor trauma 3 mo prior to the consultation. Physical examination revealed a fusiform swelling of the proximal phalanx of the right thumb without ecchymosis, pain, or tenderness. Joints were not involved and showed full range of motion. Laboratory examinations showed normal concentrations of serum calcium and phosphorous. X-ray examination revealed a multiloculated cystic defect with sparing of the cortex (Fig. 5). An enchondroma or aneurysmal bone cyst was suspected. The patient underwent curettage of this lesion with bone grafting 3 mo after presentation. Histologic examination revealed a stroma of interlacing spindle cells with numerous intermixed multinucleated giant cells and scattered inflammatory cells. Areas of hemorrhage were noted. Of particular interest were many foci of newly formed osteoid and cartilaginous material including immature cartilage (Fig. 6). At this time a diagnosis of giant cell reparative granuloma was made. Consultants suggested chondromyxoid fibroma and GCRG with secondary aneurysmal bone cyst formation. The location, the fibrous stroma with numerous giant cells, and the absence of hemorrhagic cystic degeneration favored GCRG.

Six mo after surgery, this patient again presented with swelling of the proximal phalanx of the first digit, and a hemiphalangectomy with autologous cortical bone grafting was performed. Histologic examination revealed a stroma of interlacing spindle cells with numerous intermixed multinucleated giant cells and scattered inflammatory cells. Areas of hemorrhage were noted. Of particular interest were many foci of newly formed osteoid and cartilaginous material including immature cartilage (Fig. 6). At this time a diagnosis of giant cell reparative granuloma was made. Consultants suggested chondromyxoid fibroma and GCRG with secondary aneurysmal bone cyst formation. The location, the fibrous stroma with numerous giant cells, and the absence of hemorrhagic cystic degeneration favored GCRG.

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cancellous bone graft was performed. Histology at this time revealed interlacing spindle cells with intermixed multinucleated giant cells. There were several areas of new bone formation. Some of the trabecular bone showed a central zone of chondroid-like material surrounded by osteoid. The lesion extended to the epiphyseal plate. This recurring lesion was considered typical of a giant cell reparative granuloma. Four years later, upon admission for an unrelated condition, there was no evidence of further complications or recurrence.

Case 3. An 8-year-old girl presented with a mass on the distal left fifth digit, which had been present for 3 to 4 mo. The medical history was noncontributory. Physical examination revealed a fusiform enlargement of the left fifth middle phalanx without erythema. Range of motion at the interphalangeal joint of the digit was intact and sensation was normal. X-rays showed a multiloculated cystic lesion in the middle phalanx with a non-distended intact cortex. An enchondroma was suspected. Surgical curettage and bone grafting were performed. Histologic examination revealed fibroconnective tissue with extensive osteoid formation and scattered multinucleated giant cells (Fig. 7). A diagnosis of giant cell reparative granuloma was made. During the following two years, there has been no recurrence.

Discussion

The radiologic and histologic diagnosis of giant cell reparative granuloma can be misleading. Demographic data and clinical presentation are suggestive at best. Reported age have ranged from 3 to 76 yr [4]. Gender distribution has been variable, with reports of male predominance [3,4], female predominance [1,5], and

Fig. 6. Cartilage and chondromyxoid islands are uncommon but well-documented features of GCRG (H&E, x100).

Fig. 7. Focally exuberant, woven bone formation can occasionally be seen, and may raise the question of osteoid osteoma or bone-forming neoplasms (H&E, x100).
an equal male to female ratio [2]. The clinical presentation often includes pain or swelling, and the history may include trauma [2]. Most of these lesions occur in the phalanges of the hand, with a smaller proportion in metacarpal and metatarsal bones [3-5].

The three cases reported here are female and their ages range from 8 to 15 yr. Two patients presented with pain and swelling, and the third with a mass lesion. Two reported a history of trauma. In two cases, the lesion occurred in a phalanx of the hand; in the other case, the lesion occurred in a metatarsal. There was one recurrence in this series.

Even with the aid of demographics and clinical history, the radiologic and histologic diagnosis of GCRG can be challenging. The typical radiographic appearance is an expansile lucency with an intact but thinned cortex [1-8]. A fracture may be present [2,5]. The characteristic histology includes a cellular fibrous stroma with irregularly distributed, multinucleated giant cells, many of which occur in clusters associated with foci of hemorrhage. Occasionally, mononuclear inflammatory cell infiltration is present, and osteoid formation is often found [1-8]. GCRG is similar to lesions of the skull and jaw and the differential diagnosis includes giant cell tumor, brown tumor of hyperparathyroidism, aneurysmal bone cyst, and nonossifying fibroma. Our cases include unique histologic features that expand the differential diagnosis.

GCRG must be distinguished from giant cell tumor of bone. The radiologic appearance of giant cell tumors frequently shows epiphysial involvement and is more likely than GCRG to include cortical damage or extension to soft tissue [4,8]. Histologically, giant cell tumors are less spindly and the stroma is not fibrous. The giant cells typically have more nuclei, are rounder, blend into the cellular background, and do not show clustering around areas of hemorrhage as in GCRG. Giant cell tumors are less likely to have osteoid; however, presence of a fracture may elicit a reactive fibrosis and osteoid formation, making the distinction between the two entities more difficult [3,4].

The brown tumor of hyperparathyroidism can histologically resemble GCRG, and separation of the two requires analysis of serum calcium and phosphorus concentrations, and serum alkaline phosphatase activity [1,2,6]. Radiographically, one would expect more generalized diminution of skeletal density in cases of hyperparathyroidism, although a solitary skeletal lesion may be the only manifestation [3,5].

Aneurysmal bone cyst (ABC) is another lesion that may appear similar to GCRG radiologically and histologically. Radiologically, an ABC may present as an expansile lytic lesion similar to GCRG. Histologically, it may have a solid component that contains giant cells with a fibrous stroma and osteoid formation. The main difference is the overall architectural organization of the lesion. Typically, ABC contains blood-filled vascular spaces surrounded by the cellular component, a finding not seen in GCRG. ABC may be a primary lesion or secondary to other lesions [5].

A nonossifying fibroma has a different radiographic appearance and location; however, it may show a histologic appearance similar to GCRG. Nonossifying fibroma is a term reserved for cortical lesions of the long bones, and occurs primarily in skeletally immature patients [3,6]. A nonossifying fibroma can exhibit a xanthogranulomatous reaction amidst the histologic features seen in GCRG [9].

The unique features in our three cases are the presence of cartilage, immature chondromyxoid tissue, and extensive bone formation, occasionally associated with nuclear atypia. These microscopic features provoke a different set of differential diagnoses, which may include osteogenic sarcoma, osteoid osteoma, chondromyxoid fibroma, chondroblastoma, and enchondroma. Chondromyxoid fibromas are rare lesions that generally occur during the second or third decade of life. Histologically, they typically have a lobulated appearance with a sparsely cellular myxoid center, around which is a hypercellular area that contains scattered giant cells. They can be associated with an aneurysmal bone cyst and can resemble GCRG. Histologically, chondroblastomas typically contain a mixture of giant cells and mononuclear cells with chondroid formation and "chicken wire" calcification. Secondary aneurysmal bone cysts may occur with this lesion as well [5-8]. As with GCRG, enchondromas typically appear as lytic lesions with a thinned cortex on radiographs. Histologically, they are almost exclusively composed of islands of cartilage with only a small amount of fibrohistiocytic and giant cell stroma.

In conclusion, giant cell reparative granuloma involving the small tubular bones of the hands and
feet is a rare entity and one that may be subject to misdiagnosis. The three cases reported here demonstrate the histologic variability of this lesion, some of its less common features, and the diagnostic challenges that it presents for histological examinations with frozen and permanent sections. Long-term follow-up in the three cases showed a benign course, highlighting the fact that the differentiation of GCRG from more aggressive lesions is important in order to prevent mismanagement.

References