Mazabraud's Syndrome: Intramuscular Myxoma Associated with Fibrous Dysplasia

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Abstract
Mazabraud's syndrome is a rare disease known as the association of intramuscular myxoma with fibrous dysplasia. The number of reported cases in 2004 is 55. Myxomas generally occur as multiple masses and fibrous dysplasia most commonly appear with its polyostotic form. Both lesions tend to involve the same anatomical region. Patients usually present with a painless mass with a history of long duration due top lack of symptoms. Most fibrous dysplasias are asymptomatic while some may appear with pain, skeletal deformities or fractures. Generally fibrous dysplasias occur during the growth period and the myxomas appear during adult life. The relationship between fibrous dysplasia and myxoma remains unclear, where an underlying localized error in tissue metabolism has been proposed. Molecular genetic analysis has shown activating mutations in GNAS1 gene. Several benign lesions as well as richly myxoid malignant lesions may be confused with myxoma. Histopathologic examination should be carried out to exclude malignancy. Treatment is dependent on the extent of the lesions. Malignant transformation of myxoma is not reported, although local recurrence may be expected if incompletely resected. While sarcomatous transformation is uncommon for fibrous dysplasia, greater risk has been reported for Mazabraud's syndrome. In a patient with soft tissue mass and multiple bone lesions, it is important to recognize Mazabraud's syndrome for appropriate management of the patient.

Key words
Mazabraud's syndrome, intramuscular myxoma, fibrous dysplasia

Definition and disease name

Mazabraud's syndrome is a rare disease described as the association of single or multiple intramuscular myxomas with monostotic or polyostotic form of fibrous dysplasia. This relationship was first noted in a case of osteitis fibrosa and multiple myxomas (Henschen, 1926). Mazabraud *et al*. reviewed the literature of and proposed the existence of a syndrome characterized by intramuscular myxoma and fibrous dysplasia of bone (Mazabraud,1967).

Differential Diagnosis

Many different lesions like enchondroma, aneurysmal bone cyst, chondrosarcoma, simple bone cyst, low grade central osteosarcoma, nonossifying fibroma, osteofibrous dysplasia and medullary bone infarct are considered in radiographic differential diagnosis of fibrous dysplasia especially if the lesion is monostotic. Although in most cases fibrous dysplasia exhibits a very characteristic histologic picture,

sometimes it may be necessary to distinguish it from lesions like desmoplastic fibroma, ostefibrous dysplasia, nonossifying fibroma, and low grade central osteosarcoma. Osteofibrous dysplasia and fibrous dysplasia exhibit similar radiologic and histopathologic features. The former lesion has a predilection for the cortex of the tibia. Osteofibrous dysplasia has immature nonlamellar bone rimmed by osteoblasts. When the bone formation is limited there may be a problem in distinguishing from non ossifying fibroma. Osteosarcoma has pleomorphic cells with frequent mitosis. The distinctive trabecular pattern is not present.
Benign and malignant myxoid lesions may be confused with intramuscular myxoma. Benign tumors like myxolipoma, myxoid neurofibroma, neurothecoma, myxochondroma and nodular fasciitis may show areas resembling intramuscular myxoma. It is important to recognize richly myxoid malignant tumours like myxoid malignant fibrous histiocytoma, myxoid liposarcoma, low grade fibromyxoid sarcoma and myxoid chondrosarcoma in differential diagnosis. While low-grade malignant fibrous histiocytoma (myxofibrosarcoma) is a hypocellular lesion with abundant myxoid stroma, there is always nuclear hyperchromasia and cytologic atypia leading to a malignant tumour. Myxoid liposarcoma has a regular plexiform vasculature, stellate cells with mild cytologic atypia and lipoblasts. Low grade fibromyxoid sarcoma is another entity characterized by uniform spindle shaped cells, myxoid matrix, and swirling arrangement of tumour cells around thin walled capillaries. Myxoid chondrosarcoma is identified by nests and chords of cells with dense eosinophilic stroma in a chondroitin sulfate rich stroma (Enzinger, 2001). Awareness of Mazabraud's syndrome, especially when the myxoma is solitary, can prevent misdiagnosing a malignant mesenchymal tumour.

Incidence

Mazabraud's syndrome is rare. Individual sporadic cases have been reported. The number of reported cases in 2004 is 55.

Etiology

The relationship between the two lesions remains unclear. A basic error in tissue metabolism persistent years beyond initial growth and restricted to the regions of bony involvement has been proposed. (Wirth, 1971) Also higher incidences of minor bone abnormalities like cortical thickening, cystic translucencies, exostoses or supernumerary bones have been detected accompanying intramuscular mxyoma (Miettinen, 1985). A common, yet, undetermined denominator has been proposed to explain the origin.
Molecular genetic analysis has shown point mutations in the GNAS-1 gene encoding a signal transduction protein that regulates the cellular cyclic adenosine monophosphate level in intramuscular myxoma. (Okomato, 2000) Mutations in codon 211 were detected in five of six intramuscular myxoma cases with Mazabraud's syndrome (Faivre, 2001) The same Gsα mutations also have been detected in McCune Albright syndrome as well as in sporadic intramuscular myxoma (Schwindinger, 1992, Cohen, 2002).

Clinical Description

Intramuscular myxoma is a tumor of adult life. About two thirds of the patients are female (Iwasko, 2002). Most patients present with a painless mass usually with a history of long duration due to relative lack of symptoms. (Gianoutsos, 1990) The lesions involve the lower extremities more commonly. While intramuscular myxomas are solitary, 81% of patients with Mazabraud's syndrome have multiple myxomas (Prayson, 1993). They tend to be multiple and appear in close proximity to the region of the most severely affected bone. However a contiguous connection between a myxoma and a fibrous dysplasia has never been established. The number and size of myxoma and dysplasia lesions occur irrespective of each other.
Most fibrous dysplasia are asymptomatic. Symptoms occur many years after the presence of the lesion. Some patients present with pain, skeletal deformities, and pathologic fractures particularly for lesions of the lower extremities when not accompanying myxomas, fibrous dysplasia tends to be monostotic. Most patients with Mazabraud's syndrome present with the polyostotic form of the disease but monostotic involvement has been reported as well (Sundaram,1989). The lower extremities are most commonly affected. There is predilection for one side of the body in polyostotic form of the disease. In most cases fibrous dysplasia is noted during the growth period while myxomas become apparent during adult life. (Wirth, 1971, Blazier, 1986) Rarely multiple intramuscular myxomas are detected before the osseous lesions (Court-Payen,1997).

Radiologic findings

Radiographic appearance of fibrous dysplasia varies with the proportion of osseous and fibrous tissue. The more fibrous lesions show greater lucency exhibiting a ground glass appearance, while the osseous lesions are dense and sclerotic. Besides secondary calcifications or ossification patterns may be observed. The

borders are well defined. The cortex is usually intact, but it may be thinned due to expansive nature of the lesion. Bone scintigraphy is useful in showing the activity and multicentricity of the lesions (Hoshi,1990). Computed tomography helps to point out the extent of bone involvement (Daffner 1982) . Magnetic resonance image show homogenous moderately low signal intensity on T_1 weighted images. On T_2 weighted images the signal may be mixed or high. Signal intensity on T_1 and T_2 weighted images depend on the degree of bone trabeculae, fibrous tissue, cystic and hemorrhagic changes. The sclerotic rim is seen as a band of signal intensity on both T_1 and T_2 sequences (Jee,1996).
Plain radiographs of myxomas show nonspecific, poorly defined soft tissue masses. MRI demonstrates a well-circumscribed mass with homogenous signal intensity. T_1 weighted sequences demonstrate low signal intensity mass and T_2 weighted images show a high signal intensity mass. With contrast enhancement is proportional to the amount of solid myxoid tissue and fibrous septa. (Iwasko, 2002, Cabral, 1998).

Histopathology
Fibrous dysplasia is characterized by replacement of normal bone and marrow by tissue composed of bland fibrous tissue and irregular spicules of woven bone. Rimming of osteoblasts is not present around the bone spicules although this change may be focally encountered in areas adjacent to fracture.
Myxomas have a glistening gray-white appearance depending on the amount of myxoid material. Although they may seem well circumscribed, they infiltrate the adjacent muscles. The tumor is relatively hypocellular with abundant mucoid material and loose reticulin fibers. Vascular structures are sparse. The cells have a stellate shape with small hyperchromatic pyknotic nuclei and scanty cytoplasm (Enzinger, 2001). Some myxomas may show focal areas of hypercellularity. However absence of nuclear atypia, mitotic figures or necrosis help to rule out malignancy (Nielsen, 1998). Mucoid material stain positively for alcian blue, mucicarmine and colloidal iron. Immunohistochemical studies have shown staining for vimentin and no reaction for S100.

Treatment
Myxomas are benign. No report has been encountered describing malignant degeneration of a myxoma. Treatment is dependent on the extent of the lesions. They should be excised if pain or pressure symptoms develop. Simple local excision is sufficient. Rare local recurrence is possible with incomplete resection of the lesion (Miettinen, 1985. Silver, 2002).
Clinical course of fibrous dysplasia is variable. When the lesions are extensive the fibrous dysplasia may progress to marked deformities and fractures. The disease progresses slowly and has a favorable prognosis if the involvement is local.
Patients with multiple intramuscular myxomas should be preoperatively examined for osseous lesions. A proper histopathologic examination is necessary to exclude malignancy or metastatic tumor in an elderly patient (Kabukcuoglu, 2004). A post-operative follow up is also needed to detect other soft tissue myxomas. In a patient with multiple intramuscular tumours associated with bone lesions, recognition of Mazabraud's syndrome is important for appropriate management to avoid unnecessary wide excision and radiotherapy.
The lesions of fibrous dysplasia tend to stabilize as skeletal maturity is reached. Treatment is usually conservative and aims to prevent deformity. Bisphosphonates may be helpful in relieving pain and possibly in reconstituting lesions with normal bone (Lane, 2001). Surgical treatment is indicated for severe and progressive disease, nonunion, persistent pain or fracture of a weight bearing bone. Surgery is not necessary for an asymptomatic lesion unless there is a risk of pathological fracture. Curettage and grafting of the bone defect with autograft or allograft may result in resorption of the graft into fibrous dysplasia causing high rates of local recurrence. Curettage and bone grafting alone is best suited to lesions in non-weight bearing bones. Painful long bone lesions can be stabilized by cortical grafting or implant fixation. Expendable bones can be treated by excision. Deformity may require corrective osteotomy and internal fixation (Ippolito, 2003).
While sarcomatous transformation is uncommon in fibrous dysplasia alone, a greater risk is present for patients with Mazabraud's syndrome. Sporadic cases have been reported calling for the necessity of clinical follow up. (Witkin, 1986, Lopez-Ben,1999, Jhala, 2003).

Unresolved Questions
Involvement of the same anatomical region by dissimilar lesions remains to be a anonymity. In addition, the relationship between fibrous dysplasia and myxoma remains unclear.
Bisphosphonates have been proven to be effective in decreasing pain in fibrous dysplasia, but their effect on the course of the disease and fracture rate is not clear. Further investigations are needed for effective treatment of fibrous dysplasia.

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