Infantile Myofibromatosis

Authors: Eleftheria G Hatzidaki MD and Cristina Ch Giannakopoulou[1] M.D.
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[1]Department of Neonatology of the University of Crete, 37 Altantithos Street, 71305 Heraklion Crete – Greece. E mail: ekibolos@med.uoc.gr or hritsa@yahoo.gr

Abstract
Keywords
Disease name / synonyms
Definition / diagnostic criteria
Etiology
Clinical description
Diagnostic methods
Epidemiology
Genetic counselling
Antenatal diagnosis
Management
Unresolved questions
References

Abstract
Infantile myofibromatosis is an unusual mesenchymal disorder characterized by the proliferation of tumours in the skin, muscle, bone, and viscera. It is the most common fibrous tumour of infancy and childhood but adult case have been reported. The tumours are mainly present at birth or develop during the first weeks of life, 90% of cases lesions were noted as occurring before two years of age This disorder has two distinguishable types; the solitary type, defined by the presence of one nodule in the skin, muscle, bone or subcutaneous tissue, and the multicentric type, which can be further divided into two sub-types. The first sub-type has multicentric lesions but no visceral involvement, while in the second type, visceral involvement is present. Clinical manifestations of the disease depend on the site and number of lesions. Pain may occur and is related to compression of adjacent neural structures. The etiology of this disorder is unknown. Although it is a rare condition, it is the most common fibrous tumour of infancy. Prognosis for this disease depends on the presence of visceral involvement. For solitary and multicentric nodules with no visceral involvement, prognosis is usually excellent, with spontaneous regression of lesions. However, the presence of visceral lesions is associated with significant morbidity and mortality, which result from obstruction of vital organs, failure to thrive, or infection. Once a diagnosis has been made, observation is the treatment of choice. Surgical excision is sometimes required for obstructive or locally destructive tumours.

Keywords
Infantile Myofibromatosis, fibrous tumours, mesenchymal disorder, spontaneous regression

Disease name / synonyms

Infantile myofibromatosis (IM) is the most common fibrous disorder of infancy and early childhood (Wiswell et al., 1988). About 50% of the lesions are present at birth or shortly after and these enlarge during the first few months of life; while in almost 90% of cases lesions were noted as occurring before two years of age. This condition was first described by Stout, in 1954, as “congenital generalized fibromatosis” (Stout, 1954). In 1965, Kauffman and Stout (Kauffman et al., 1965) and others (Enzinger, 1965), further sub-divided IM into solitary, multiple, and generalized forms based on the extent of involvement. Since Stout’s report, numerous additional examples of this condition have been described in literature under various synonyms, including: “congenital multiple fibromatosis”, “multiple mesenchymal hamartomas”, “multiple vascular leiomyomas of newborn” and “diffuse

congenital fibromatosis" (Chung et al., 1981). "Infantile myofibromatosis" as a term was first coined by Chung and Enzinger in 1981, after reviewing 61 cases (Chung et al., 1981). Their purpose was to indicate the early age of onset and the myofibroblastic nature of the affected cells.

Definition / diagnostic criteria

Infantile myofibromatosis is an unusual mesenchymal disorder characterized by the development of firm, discrete nodules, varying from flesh-coloured to purple, in skin, muscle, bone, and subcutaneous tissues. These nodules are visible, raised, firm, violaceous, palpable, and range from fully moveable to relatively fixed. The nodules are usually rubbery in nature, and can vary in number from one to one hundred, and in size from 0.5 to 7 cm (Chung et al., 1981).

The disorder can be separated into two distinguishable types; the solitary form, defined by the presence of one nodule in the skin, muscle, bone or subcutaneous tissue; and the multicentric form, which can be further divided into two sub-types. The multiple form also involves bone, and the generalized form which also involves viscera (Wiswell et al., 1985; Wiswell et al., 1988). Visceral involvement has been reported as affecting approximately 35% of patients with the multicentric form of the disease, may occur in the lungs, heart, or gastrointestinal tract and may result in these organs being compromised (Chung et al., 1981; Behar et al., 1998). The bones most commonly involved are the skull, femur, tibia, spine, and ribs (Chung et al., 1981). On rare occasions the central nervous system is affected (Behar et al., 1998).

The ultra structural, histological, and immunohistochemical characteristics of IM permit its differentiation from many other benign and malignant conditions of infancy, such a neurofibromatosis, leiomyoma, hemangiopericytoma, histiocytosis x, osteoblastoma, hemangioma, lymphangioma, fibrosarcoma, metastatic neuroblastoma, fibrous dysplasia, rhabdomyosarcomal, fibrous histiocytoma, myxoma, and which may have different natural histories (Behar et al., 1988; Netscer et al., 2001).

Etiology

The aetiology of this disorder is unknown. Increased occurrence within families and identification of the disease in twins, suggests the possibility of an autosomal dominant inheritance pattern, while recessive modes of inheritance have also been postulated (Baird et al., 1976; Zand et al., 2004). The age of onset of lesions suggests that the disease may be secondary to a potential intra-uterine toxic state, during pregnancy. Intra-uterine estrogens exposure has been proposed as a possible contributing factor (Giannakopoulou et al., 1999; Counsell et al., 2002). However, a case of a male twin where one twin has IM, while the other is a healthy baby, has been recently reported (Ozturk et al., 2004). These findings do not support a role of intra-uterine estrogens exposure in the pathogenesis of this disease. Leaute-Labreze et al. reported a case of an infant with elevated levels of urinary basic fibroblast growth factor (bFGF); an angiogenic factor secreted by numerous cells, which plays a major role in tumour proliferation during the active phase of the disease, suggesting angiogenic stimulation in its pathogenesis (Leaute-Labreze et al., 2001). A case of IM has been reported involving deletion of chromosome 6, [del (6) (q12q15)]. Further studies were not done to distinguish whether the 6q deletion to the tumour or present in the germ line (Netscher et al., 2001). The report of a child with Turner syndrome treated with interferon alpha is the only report of a patient with a cytogenetic anomaly in the literature (Savasan et al., 1998).

Clinical description

Clinical manifestation of the disease and its clinical course obviously depend on the site and number of lesions. There are few clinical symptoms unless visceral involvement is present. Pain may occur and is related to compression of adjacent neural structures. Large lesions may become ulcerated. Approximately one-third of the lesions present in the head and neck, while the majority of the lesions occur cutaneously or in the skeleton. Calvarial bone involvement is common, although any bone may be affected. Solitary lesions of the orbit, calvarium and temporal bone have also been described. Visceral lesions are associated with a significant morbidity and mortality rate, which is the result of obstruction in vital organs, failure to thrive, or infection (Sybert, 1997). The central nervous system is rarely affected, but tumours can lead to severe neurological impairment (Behar et al., 1998). Spinal canal involvement with secondary bowel and bladder dysfunction and lower extremity paresis, has been reported (Schrodt et al., 1999). In a study of 61 cases of IM, Chung and Enzinger identified only one infant as having widespread lesions with visceral involvement but with no skeletal involvement (Chung et al., 1981). Counsell et al recently reported a case of an infant with multiple, widespread lesions focused subcutaneously and intramuscularly, but with no skeletal involvement (Counsell et al., 2002). About 50% of the lesions

are present at birth or shortly after and these enlarge during the first few months of life; while in almost 90% of cases lesions were noted as occurring before two years of age (Chung et al., 1981). Prognosis for this disease depends on whether visceral involvement is present. Spontaneous regression within 1 to 2 years from diagnosis is generally the natural historical course for IM lesions without visceral involvement. When death occurs it is often at birth or soon after, and is usually due to acute cardio-pulmonary failure, haemorrhage or gastrointestinal obstruction, (Chung et al., 1981; Behar et al., 1998; Giannakopoulou et al., 1999). Recently, apoptotic cell death has been proposed as a possible mechanism for this regression (Behar et al., 1998).

Diagnostic methods

Evaluation of an infant with suspected IM should include a thorough family history, physical examination, skeletal survey, ultrasound evaluation, computed tomography or magnetic resonance imaging the thorax and abdomen, while a biopsy should be performed (Thunnissen et al., 1993; Ang et al., 2004). The characteristic roentgenographic features of IM involving bones are well-circumscribed, lytic lesions with sclerotic margins. If a calvarial lesion is present, computed tomography scanning may reveal a lytic lesion causing expansion of the inner and outer tables. Central areas of calcification may also be present. Magnetic resonance imaging has also been proposed for evaluation of the extent of visceral involvement. Some tumours are better shown on computed tomography without administration of intravenous contrast medium, while others are more readily identifiable following administration of intravenous contrast medium. However, computed tomography may underestimate the true extent of the disease (Counsell et al., 2001).

Although radiographic findings are helpful, an open biopsy is necessary for a clear diagnosis of IM. The histological features of IM can be quite variable resulting in broad diagnosis differentials. Solitary and multicentric variants do not differ regarding their histological appearance, which is that of collagen producing, spindle-shaped cell bundles, staining focally as both smooth muscle and fibroblasts (Wiswell et al., 1985). Areas of calcification have been reported in literature, which generally occur in lesions with necrosis (Soper et al., 1993).

Electron microscope investigation reveals fibroblasts and smooth muscle-type cells, a fact, which supports the view of hamartomatosis (Lin et al., 1971). Recent reports have suggested a histogenic relationship between IM, congenital fibrosarcoma, and congenital hemangiopericytoma (Variend et al., 1995; Schrodt et al., 1999). Variend et al suggest that these tumours represent differing stages in maturation of the same entity (Variend et al., 1995). A zoning phenomenon is present histologically. Peripheral spindle-shaped cells arranged in bundles blend centrally into less differentiated round or polygonal cells arranged in sheets. The spindle cells of IM have the ultra structural and immunohistochemical characteristics of myofibroblasts, staining positive for vimentin and a smooth muscle actin, but negative for desmin. The cells are also negative for S-100 protein, allowing their differentiation from more immature histiocytes (Iijima et al., 1999; Netscher et al., 2001). It also has been reported that in addition to necrosis and calcification, nuclear atypia may be present in this entity. As a result, IM is occasionally misdiagnosed as a soft tissue malignancy, such as fibrosarcoma or rabdomyosarcoma. Immuno-staining for vimentin, and actin can be helpful in distinguishing between IM and these entities (Behar et al., 1998). Progressive cell differentiation has been offered as a possible explanation for the spontaneous regression of solitary lesions, and as a hypothesis is more commonly accepted than the previously proposed apoptosis (Iijima et al., 1999; Netscher et al., 2001).

Epidemiology

Infantile myofibromatosis usually arises in childhood, in the neonatal period or soon after, but it has occasionally been described in older children and young adults (Raney et al., 1987). Wiswell et al. report that there is a male preponderance (62%), both for the solitary and the multicentric forms of the disorder (Wiswell et al., 1985). On the other hand, Chung and Enzinger report a female infant preponderance in terms of the multicentric variant of the disease (Chung et al., 1981). The solitary form accounts for approximately 75% of cases. Although it is a rare condition it is the most common fibrous tumour of infancy (Counsell et al., 2002). In the past, sporadic cases have been reported of infants with visceral involvement who survived (Hatzidaki et al., 2001). Eighteen cases of pulmonary involvement were reported by Soper in his review. Of these only four survived. He reports a case of an identical twin neonate with involvement of long bones, tongue and liver, which regressed by 18 months (Soper at al., 1993). From 155 patients that were reported in 1985, 29 presented multiple lesions with visceral involvement. 22 of these infants (76%) died at birth or soon after, usually due to cardiopulmonary or gastrointestinal complications (Wiswell et al., 1985). Up to 1997,

there were at the very least 231 reported cases. One hundred and seventeen (51%) of these were multicentric, and 43/117 showed visceral involvement (18,61%). In the group with visceral involvement 32/43 (76%) patients died. On the other hand, the mortality rate was zero in the solitary tumour group, and very low (1/75) in the multicentric group without visceral involvement (Zeller at al., 1997). From research of the existing literature available to us, it was difficult to clarify the percentage of cases of infantile myofibromatosis with visceral involvement, where no treatment procedure was followed, which regressed spontaneously.

Genetic counselling
Genetic counselling should be provided to the parents as IM may be a hereditary condition.

Antenatal diagnosis
Infantile myofibromatosis appears to originate *in utero*. Cases of this disease have recently been reported in literature that was identified on prenatal ultrasound examination (Nishioka et al., 1999; Kubota et al., 1999).

Management
Once a diagnosis has been made, observation is the treatment of choice. Surgical excision is sometimes required for obstructive or locally destructive tumours (Behar et al., 1998). Resection of multiple lesions is not indicated unless functional impairment ensues or vital organs are affected. Complete excision is often curative with a reported recurrence rate of 7-10% (Behar et al., 1998). Prognosis is worst for involvement of the lungs and central nervous system (Netscher et al., 2001). In aggressive cases, limited success has been achieved by treatment with radiotherapy, steroid injection, and chemo RA therapy (Gandhi et al., 2003; Johnson et al., 1997). Alpha interferon has been administered to one patient with IM (Savasan et al., 1998). The anti-estrogens agent tamoxifen has also been used in one patient with IM, but no improvement was seen with its use (Coffin et al., 1995). Evaluation of the efficacy of these regimens is difficult in a disease with the tendency to spontaneous regression. Periodic computed tomography scans or other imaging studies are not necessary unless clinical progression of the disease is suspected.

Unresolved questions
A case has recently been reported of elevated urinary basic fibroblast growth factor levels during the active phase of the disease, suggesting angiogenic stimulation in its pathogenesis. This hypothesis suggests a possible use for anti-angiogenic factors in the treatment of myofibromatosis to control tumour proliferation, as well as interferon-alpha. The possible use of bFGF is also interesting as a marker of proliferation in systemic IM, to monitor the efficacy of treatment or in the follow-up of spontaneous regression (Leaute-Labreze et al., 2001) However, there is no consensus between chemotherapy, interferon therapy, radiotherapy, or even if medical therapy is indicated in severe cases of this disease. These unresolved questions regarding appropriate intervention, most likely reflect the fact that we still do not understand the etiology, the pathogenesis and the mechanisms of regression for IM.

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