Cytologic-Pathologic Correlations

Mitotically active deep juvenile xanthogranuloma

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Abstract

Juvenile xanthogranuloma is a relatively rare cutaneous tumor of histiocytic origin, occurring mainly in neonates, children, and young people in the first 2 decades of life. An occurrence in adults is rare. Very rare is also a “deep” subcutaneous and intramuscular localization of this tumor that is called in such case as “deep juvenile xanthogranuloma.” A very uncommon variant of this tumor is the so-called mitotically active xanthogranuloma, which was described in the literature only in a single case. We present an interesting case of the mitotically active intramuscular juvenile xanthogranuloma of the upper arm in a 28-year-old woman. Before surgical excision, the tumor was examined by fine-needle aspiration biopsy. A diagnosis of deep malignant melanoma or alveolar rhabdomyosarcoma was considered. One year after the total excision, the patient is free of disease. In the presented case, we emphasize cytologic-histologic correlation. In the differential diagnosis, we considered especially an atypical diffuse giant cell tumor of tendon sheaths and joints (extra-articular pigmented villonodular synovitis) and some rare types of soft tissue leiomyosarcoma, such as epitheloid leiomyosarcoma and leiomyosarcoma with prominent osteoclast-like giant cells.

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1. Introduction

Juvenile xanthogranuloma (JXG) is a relatively rare benign histiocytic cutaneous tumor that occurs typically in young patients in the first 2 decades of life [1-9]. Juvenile xanthogranuloma rarely affects adults [1-7,9]. A less common is subcutaneous and intramuscular localization of this tumor, that is, so-called deep JXG [1-7,9]. A very rare is a mitotically active deep JXG, of which only a single case was reported by Miguélez et al [5] in 2002. Here we report an interesting case of mitotically active intramuscular JXG of the left upper arm in a 28-year-old woman. The tumor was of nonlipidized type. It was examined before the surgical excision by fine-needle aspiration (FNA) biopsy. One year after the complete excision, the patient is free of disease. To our knowledge, only 2 well-documented JXGs examined by FNA were described [6,10], and only one case of deep JXG was verified histologically after the cytologic examination and surgical excision [10].

2. Materials and methods

The tumor was examined before the surgical excision by FNA, using a standard method with a special pistol. The smears were fixed by air and were stained by May-Giemsa-Grunwald stain. The tissue was fixed in 4% formalin and processed routinely. All tumor tissues were paraffin-embedded. The sections were stained with hematoxylin and eosin stain and Pearl’s histochemical stain for iron.

Immunohistochemical studies were performed on formalin-fixed, paraffin-embedded sections using the following antibodies: \(\alpha\)-muscle–specific actin (HHF-35, 1:50),

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**3. Results**

A 28-year-old and otherwise healthy woman presented with 2-month slowly growing painless mass of the left upper arm. Ultrasonography showed intramuscular tumor in the distal part of the biceps brachii muscle. The lesion was examined by FNA biopsy, and, 2 days after the cytopathologic diagnosis of malignancy, a wide tumor excision was performed. The resected intramuscular tumor measured 2.5 cm in diameter, and had a soft consistency and strong yellow and homogenous cut surface. Fibrous capsule was not seen, but the tumor was circumscribed and did not show grossly visible infiltration of adjacent muscle tissue. A patient is free of disease 1 year after the surgery.

The smears obtained by FNA biopsy were very cellular. They contained mainly numerous epitheloid cells of intermediate size, with eccentric nuclei devoid of nuclear pleomorphism. Numerous nuclei had inconspicuous nucleoli, and some of them also showed less conspicuous intranuclear inclusions of cytoplasm. The cytoplasm was abundant, and it was of more dense appearance in the central parts of cells. Some mononuclear histiocytes and scattered giant multinuclear cells were found in the smears (Fig. 1). A

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**Fig. 1.** Cellular smear by FNA biopsy mimicking primary epithelioid malignant tumor (May-Giemsa-Grünwald stain).

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**Fig. 2.** Mitotically active deep juvenile xanthogranuloma. (A) Tumor with well-circumscribed margin, without infiltration into surrounding skeletal muscle (hematoxylin and eosin). (B) The tumor consists of numerous mononucleated epithelioid cells, foamy macrophages, and multinucleated giant cells of Touton type (hematoxylin and eosin). (C) High cellularity and numerous typical mitoses.
peritheliomatous growth pattern was focally well visible. A cytologic diagnosis of primary epitheloid malignant tumor, most probably of epitheloid melanoma or alveolar rhabdomyosarcoma, was suggested.

Histologic examination revealed intramuscular, well-circumscribed, non-encapsulated, very cellular and solid tumor, with minimal formation of intercellular matrix/fibers (Fig. 2A). The tumor consisted of numerous mononuclear epitheloid cells with abundant and strongly eosinophilic cytoplasm, with some intranuclear inclusions of the cytoplasm. In this dominant epitheloid cell population, less numerous, smaller, round to ovoid synovial-like cells with paler nuclei were scattered. In addition, sheets of voluminous foamy macrophages with intracytoplasmatic granulations and some multinucleated giant cells of both osteoclast-like and Touton type were seen through the tumor (Fig. 2B). Mitotic rate varied from 15 to 20 typical mitotic figures per 10 high-power field (HPF) (Fig. 2C). The tumor contained no necrosis, and it was sharply demarcated from an adjacent muscle tissue. Histochemical Pearl’s stain for iron was negative in the tumor. Immunohistochemically, mononucleated epithelioid cells were diffusely positive for desmin (Fig. 3A) and focally positive for vimentin. Foamy macrophages were positive for CD68. Tumor cells were negative for cytokeratins, EMA, HMB-45, CD34, CD117, S-100 protein, actins, h-caldesmon, and myogenin. Positivity for Ki-67 was seen in 15% of the tumor cells (Fig. 3B). A diagnosis of mitotically active intramuscular (deep) juvenile xanthogranuloma was rendered.

4. Discussion

Juvenile xanthogranuloma, described originally by Adamson et al in 1905 [1], is a relatively rare histiocytic tumor of the skin. It occurs typically in the first 2 decades of life, and predominantly in male patients [1-9]. Occurrence of JXG in adults (so-called adult type of JXG) is rare [4,9,11]. Juvenile xanthogranuloma is usually solitary and located in the head and neck region (so-called superficial JXG). Solitary JXG was rarely observed in subcutaneous and/or skeletal muscle tissue, and such form was labeled as “deep JXG” [1-12]. Deep JXG is typically located in the trunk and extremities [2-4,7,11,13]. A less frequent form of JXG is so-called systemic JXG with multiple cutaneous, subcutaneous, and visceral lesions and with various clinical symptoms [1,2,4,7,14]. In our case, a higher age of the patient and a deep localization of the tumor represent relatively unusual clinical features, and, therefore, the diagnosis of JXG was understandably not suggested by clinical examination.

Regarding cytologic features of JXG, we are aware of only 2 well-documented cases of JXG examined by FNA biopsy before surgical excision [6,10]. In the report of Barroca et al [10], a congenital, deep intramuscular JXG was located in the neck region of the newborn. The smears were very cellular and contained granulomatous clusters of numerous isolated isokaryotic histiocytes and sporadic multinuclear cells. Polynuclears and necrotic debris were seen in a background. Histologic examination confirmed so-called deep JXG. Mohindroo and Sharma [6] described a case of superficial JXG that had been located in the shoulder of a 3-year-old girl. However, the tumor was not excised and verified histologically because it regressed spontaneously. The smears contained numerous histiocytes with eosinophilic vacuolated cytoplasm, less numerous spindle-shaped fibroblasts, and giant multinucleated Touton-type cells. Numerous interspersed lymphocytes, eosinophils, and polymorphonuclear leukocytes were seen in the background of the smears [6]. Thus, the cytologic features in both cases were similar to those seen in the present tumor. In regard to distinction from any malignant epitheloid tumor by cytologic examination, we think that most valuable features are represented by the absence of “true” nuclear atypia and by

Fig. 3. Immunohistochemical results. (A) Diffuse positivity for desmin. (B) Immunohistochemical stain for Ki-67 (MIB1) demonstrates relatively high proliferation of the tumor cells (hematoxylin and eosin, streptavidin-biotin complex method [SABC] technique).
the finding of mixture of uninucleated histiocytoid cells and multinucleated cells. High cellularity of the smears should not be interpreted as a malignant feature. Histiocyte-like and/or multinucleated cytormorphology are commonly seen by cytologic examination of various malignant tumors. However, malignant tumors with such malignant histiocytoma-like morphology are usually of higher grade, and thus they show well-visible and (well-interpretable) nuclear atypia and pleomorphism. Among benign tumors composed of histiocytoid uni- and multinucleated cells, cytologic features similar to those of JXG are seen especially in giant cell tumor of tendon sheaths and joints (GCTJS). In the cases of GCTJS examined by FNA biopsy [14,15], the smears were very cellular and contained numerous mononuclear round to ovoid histiocytes. These cells were isolated or arranged in small solid clusters in a dirty background. In addition, less numerous isolated giant multinucleated cells with pigmented cytoplasm were found. Mononucleated cells showed round nuclei, inconspicuous nucleoli, and moderately eosinophilic or pigmented cytoplasm. The smears in our case showed very similar features. However, the cells were not pigmented in contrast with the cells of typical GCTJS.

Histologically, typical cutaneous JXG consists of mononuclear cells, foamy macrophages, multinucleated Touton-type cells, and spindle-shaped fibroblasts. Among these cells, a few eosinophils, lymphocytes, and sometimes also plasmocytes are scattered. The mitotic rate ranges from 0 to 2 typical mitoses per 10 HPF. More numerous mitoses in JXG are not common [1-7,10,16]. Rarely, JXG is devoid of mononucleated cells and contains only nonlipidized multinucleated cells, sometimes with more eosinophilic cytoplasm. This form is called nonlipidized JXG [1-3,17] or mitotic form of JXG [9]. Nonlipidized form of JXG contains usually numerous mitoses, especially when the lesion is ulcerated [5]. Immunohistochemically, superficial JXG is typically positive for vimentin, CD68 (strongly with PG-M1 clone, weakly with KP-1 clone) [7], lysozyme, and α-1-antichymotrypsin [1-4,6,7,9,10]. Sometimes it expresses MAC-387 [9] and factor XIII-a, and, quite rarely, expressions of CD31, α-1-antitrypsin [2], S-100 protein [2-4], HHF-actin [3,7,9], and, sporadically, of fascin, CD14, and CD163 [10] were described [2-4]. In typical cases, the tumor is negative for α-smooth muscle actin, S-100 protein, EMA, cytokeratins, HMB-45, and desmin [1-4,7,9,10]. Reactivity for desmin was not described in JXG before, to our knowledge, and it is difficult to explain it. The staining was diffuse and quite weak, and immunostains for actins and h-caldesmon were negative. Therefore, we think that this desmin reactivity does not reflect any myofibroblastic or myoid dendritic cell differentiation. As the positivity was mild, we suppose that it was caused probably by endogenous peroxidase activity or by cross-reactivity.

Deep form of JXG, firstly described by Janney et al in 1991 [3,12], shows morphology of common JXG except that it often lacks the multinucleated Touton-type cells [2] and that it contains higher number of mitoses [2,3,5,7,11-13]. The tumor infiltrates commonly a skeletal muscle. An interesting case of deep JXG with unusually high mitotic activity was described by Miguélez et al [5] in 2002. This tumor occurred in the shoulder region of a 2-year-old girl. Histologically, it was non-encapsulated intradermal tumor with focal infiltrative growth into the subcutaneous adipose tissue. The tumor consisted of epitheloid histiocytes with some foamy macrophages and multinucleated Touton-type cells. The mitotic rate was 23 typical mitoses per 10 HPF. Thus, this tumor showed deep location, epitheloid cytormorphology, and high mitotic activity, which were all features similar to those seen in our case. Behavior of the deep or mitotically active JXG is more aggressive in comparison with “common” JXG [10,13].

Whereas histologic differential diagnosis of superficial JXG includes various histiocytic lesions of the skin [1,6,7,9], reported deep JXGs needed to be differentiated mainly from deep malignant fibrous histiocytoma and from cellular subcutaneous neurogenic tumors, such as neurofibroma and cellular schwannoma [3]. Differential diagnosis of superficial JXG includes Langerhans cell histiocytosis, papular xanthoma, spindle-cell xanthogranuloma, xanthoma disseminatum, progressive nodular histiocytosis, generalized eruptive histiocytosis, benign cephalic histiocytosis, multicentric reticulohistiocytosis, Rosai-Dorfman diseases, and hemorraghic histiocytosis [1,6,7,9]. Histologic differential diagnosis of deep JXG includes mainly deep malignant fibrous histiocytoma and cellular subcutaneous neurogenic tumors, such as neurofibromas and cellular schwannomas [3]. In the differential diagnosis of our case, we considered mainly giant cell tumor of tendon sheaths and joints (GCTSJ), especially its so-called atypical diffuse form [18-23]. Like mitotic JXG, atypical diffuse GCTSJ contains mono- and multinucleated cells with histiocytic appearance and numerous mitoses. However, atypical diffuse GCTSJ is typically located closely to large joints, and it shows infiltrative growth pattern. The histologic features of JXG and atypical diffuse GTSJ are quite similar, except of the presence of the typical larger dendritic cells in atypical diffuse GTSJ. These cells show broad eosinophilic cytoplasm, large vesicular nuclei, and occasional intranuclear pseudoinclusions, and, interestingly, they are positive for desmin [23,24]. Regarding desmin reactivity, it was seen also in our case, and this feature accentuated the similarity with GTSJ. However, the present lesion differs from GTSJ by predominant Touton-type morphology of giant cells (the giant cells in GTSJ are predominantly of osteoclast-type) and by the absence of hemosiderin, which was confirmed by negativity of stain for iron. Desmin positivity was mild in our case, and it was seen in both uni- and multinucleated cells without dendriform cytormorphology, whereas in GTSJ, the positivity is strong and the desmin-positive cells are usually dendriform, with long processes that interdigitated between adjacent desmin-negative round cells [23,24]. In addition, epitheloid leiomyosarcoma [8] and leiomyosarcoma with osteoclast-like cells [25] were included in the differential
diagnosis because numerous tumor cells were of epitheloid shape and the multinucleated cells were present. In contrast with JXG, both of these leiomyosarcoma show, although focally, a distinctive fascicular growth pattern of spindle-shaped cells with eosinophilic cytoplasm and with typical cigar-shaped nuclei. Nuclear atypia is usually more striking and some mitotic figures can be by atypical. Immunophenotypically, JXG and leiomyosarcoma show some overlap, but leiomyosarcoma tends to express the smooth muscle markers (actins, desmin, h-caldesmon) more strongly.

In conclusion, we described an uncommon and interesting case of juvenile xanthogranuloma. Unusual features causing diagnostic difficulty were as follows: an occurrence in the adult patient, localization in skeletal muscle (deep JXG), and nonlipidized cytomorphology with high mitotic activity. Histologically, the tumor mimicked especially atypical giant cell tumor of tendon sheaths and joints, epithelioid leiomyosarcoma, and leiomyosarcoma with osteoclast-like cells [8,19,23,25]. In addition, we described cytologic finding in deep mitotically active JXG, which were not reported before, to our best knowledge. Pathologist should be aware of deep and mitotically active JXG in adult, especially because the tumor can strongly mimic some malignant lesions by both cytologic and histologic examinations.

References