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Deep Juvenile Xanthogranuloma

Subcutaneous and Intramuscular Forms

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Juvenile xanthogranuloma occurring in soft tissue is rare and has received little attention. This report describes cases of deep juvenile xanthogranuloma occurring in the soft tissues of three children. Each tumor was a solitary lesion that arose, respectively, in the superficial skeletal muscles of an 8-month-old girl, the subcutis of the scalp of a 3-month-old boy, and the subcutis of the forehead of a 10-year-old girl. Two lesions were grossly firm, tan-yellow, and homogeneous. Histologically, the subcutaneous lesions were relatively circumscribed; the third lesion infiltrated muscle and contained widely separated skeletal muscle fibers. All lesions showed sheets of uniform amphophilic or acidophilic cells with occasional eosinophils and rare Touton giant cells. In two cases and in cutaneous controls, positive immunoperoxidase stains (HAM-56, HHF-35, and vimentin) supported macrophagic-myofibroblastic differentiation. S-100 protein, MAC-387, and factor XIIIa were negative. Electron microscopy in one case also supported macrophagic-myofibroblastic differentiation. Langerhans granules were absent. Follow-up of 7, 6, and 5 years indicated no recurrences. The differential diagnosis includes deep fibrous histiocytoma and cellular subcutaneous neural tumors.

Key Words: Juvenile xanthogranuloma—Skeletal muscle—Subcutaneous tissue—Touton giant cell, Xanthogranuloma.

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Juvenile xanthogranuloma (JXG) is the most common "xanthomatous" lesion occurring in infancy. Historically, JXG was described as a benign, self-limited, regressing, fibrohistiocytic lesion of infancy and childhood, originally named "congenital xanthoma multiplex" (1) in 1905, when Adamson observed multiple cutaneous cephalic, nuchal, and truncal lesions in a 2.5-year-old boy. The lesions were later termed "nævo-xanthomata" (20), but the name was expanded to "nævo-xantho-endotheliomata" in McDonagh's detailed description of lesions from five patients in 1912 (21). The endothelial nature of the lesion was subsequently questioned by several authors (2,17,26), as it was thought that the xanthoma cell, not the endothelial cell, was probably responsible for production of the lesion. The term "juvenile xanthogranuloma" was proposed by Helwig and Hackney in 1954 (14) also because of their doubt concerning its neoplastic and endothelial nature.

JXG is usually cutaneous, affecting both sexes equally, and no serum lipid abnormalities are present. Lesions are present from birth in 20% but usually develop between 6 and 24 months of age. Adults are affected in approximately 15% (7,11, 24,30,31). The lesions are usually located on the head and neck but may be found elsewhere on the skin, including periorbital tissues (34). The ratio of solitary to multiple lesions is approximately 2:1; the latter may occur in agminated crops. Rarely, visceral organs may be involved, but many of these cases have been poorly documented. The disease is usually self-limited and, with rare exception, undergoes spontaneous involution.

The histological hallmark of JXG is the diffuse, uniform population of epithelioid cells admixed with Touton giant cells, eosinophils, and plasma cells, each of which may occur in varying proportions. Other than a few studies with nonspecific

markers such as α-1-antichymotrypsin, (8,27) little is known about the immunophenotype of JXG. Previous ultrastructural studies have supported fibrohistiocytic differentiation (12,25,27).

Only brief mention has been made of the occurrence of JXG presenting as a soft tissue lesion (9,15,30). Because of the lack of definition of this lesion in soft tissue, we present the clinicopathological findings in three patients with deep, nonvisceral juvenile xanthogranuloma (DJXG) and describe the clinical, light microscopic, immunohistochemical, and ultrastructural features that allowed us to characterize these lesions.

MATERIALS AND METHODS

All tissues were fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin. Tissues from two patients were subjected to special studies, including histochemistry and immunohistochemistry; one (case 2) was examined ultrastructurally. The histochemical stains included reticulin, elastic, iron, and Leder stains. The immunohistochemical stains used are given in Table 1 (4,10,13,16,18,19,23,28,29,32). For purposes of comparison, histochemical and immunohistochemical stains were also performed on tissue from two cases of typical cutaneous juvenile xanthogranuloma.

Ultrastructural analysis of case 2 was performed on formalin-fixed tissue, postfixed in 1% osmium tetroxide and cacodylate buffer, embedded in Spurr resin (in block staining) with alcoholic uranyl acetate, and cut and stained with lead citrate.

RESULTS

Clinical Features

There were three patients: an 8-month-old girl, a 3-month-old boy, and a 10-year-old girl. Each had a solitary, deep-seated lesion of the back, scalp, and forehead (Table 2). None of the children had any evidence of cutaneous, ocular, or systemic lesions, nor was there any family history of hyperlipidemia or lipid disorders. Treatment of all lesions was effected by simple local excision. Follow-up of 7, 6, and 5 years, respectively, revealed no evidence of local recurrence, even though two of the lesions were incompletely excised. There has been no appearance of other cutaneous, soft tissue, or visceral lesions in any child, and an extensive ophthalmic examination performed (secondary to trauma) on patient 1 was normal except for a traumatic corneal abrasion.

Pathological Features

Grossly, one of the nodules was intact, as if it was shelled out of the subcutaneous tissues; it measured between 1 and 2 cm in greatest dimension. The other two, including the intramuscular lesion, were fragmented and were probably incompletely excised. The cut surface of all lesions was firm, yellow-tan, and showed a circumscribed border. There was no attachment to the overlying skin.

Microscopic sections of the subcutaneous lesions showed relative circumscription (Fig. 1); despite this, the intramuscular lesion involved the skeletal muscle, isolating individual fibers (Fig. 2). The growth pattern was characterized by uniform sheets of foamy or acidophilic cells that exhibited abundant cytoplasm and bland vesicular nuclei (Fig. 3); there were inconspicuous nuclear folds and grooves. In some areas, clusters of these cells resembled a nodular granulomatous infiltrate; occasional Touton giant cells were seen (Fig. 4). Scattered clusters of eosinophils, sparse plasma cells, and occasional lymphocytes were also present. Some areas showed minimal fibrosis with thin col-

TABLE 1. *Antibodies used*

Antibody	Type	Dilution	Source	Specificity	Ref
HAM-56	Mono	1:800	ENZO	Monocytes, macrophages	13
HHF-35	Mono	1:1,000	ENZO	Muscle	32
Vimentin	Mono	1:10	DAKO	Cells of mesenchymal nature	18
MAC-387	Mono	1:100	DAKO	Monocytes, macrophages	10
Factor XIIIa	Poly	1:200	Calbiochem	"Fixed" connective tissue cells	23
α-1-Antichymotrypsin	Poly	1:500	DAKO	Nonspecific	19
α-1-Antitrypsin	Poly	1:500	DAKO	Nonspecific	29
Lysozyme	Poly	predilution	DAKO	Nonspecific	29
S-100 Protein	Poly	predilution	Biomeda	Neural, myoepithelial, others	16
Factor VIIIrag	Poly	1:200	DAKO	Endothelial cells, megakaryocytes	4

All stains were performed via the avidin-biotin-complex method (28).

TABLE 2. *Clinical data, deep juvenile xanthogranuloma*

Patient	Age	Sex	Duration	Location	Size (cm)	Clinical diagnosis	Follow-up (years)
1	8 mo	F	?	Back, superficial muscles	1.5	Nodule	7
2	3 mo	M	Congenital	Scalp, left parietal, subcutaneous	1.2	Sebaceous cyst	6
3	10 yr	F	?	Forehead, subcutaneous	2	Cyst	5

lagenous septa. Comparison with the control cases of cutaneous juvenile xanthogranuloma showed several minor histopathological differences in the deep form: prominent circumscription, fewer Touton-type giant cells, and abundant eosinophils.

Reticulin stain outlined the delicate capillary network within the nodule; variable numbers of fine reticulin fibers were interspersed among the tumor cells, containing them in small clusters (Fig. 5). The Leder stain highlighted the pericapillary and intranodular mast cells. The elastic and iron stains were negative.

Results of the immunohistochemical stains on two of our patients with DJXG and cutaneous controls are summarized in Table 3. In brief, these showed diffuse cytoplasmic positivity for HAM-56, HHF-35, and Vimentin (Fig. 6). Other stains showed either minimal cytoplasmic staining or were negative.

Electron microscopy was performed on tissue from patient 2. Formalin fixation artifact was evident throughout. There was a mixture of cell types similar to the light microscopic observations. The predominant cell was a large cell with an ovoid to elliptical nucleus, usually one fenestrated nucleolus, and fine, vesicular chromatin. Cell membranes were irregular, with occasional filiform cytoplasmic projections or pseudopodia. These interdigitated with similar projections from closely apposed cells. The abundant cytoplasm contained numerous mitochondria, intermediate filaments, variable numbers of membrane-bound myelin figures, and nonmembrane-bound medium density lipid droplets (Fig. 7). Golgi and granular and vesicular smooth endoplas-

FIG. 1. Patient 2. This deep juvenile xanthogranuloma was circumscribed and homogeneous and was shelled out of the soft tissues of the scalp.

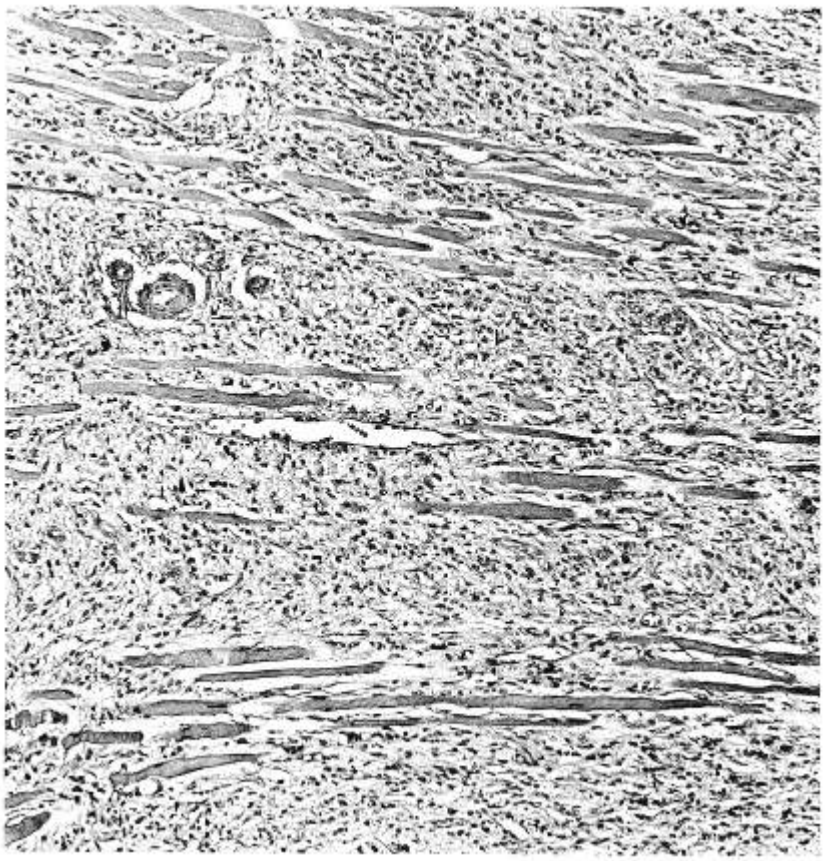


FIG. 2. Patient 1. Despite relative circumscription, this deep juvenile xanthogranuloma infiltrates skeletal muscle but was otherwise similar to examples involving only soft tissues.

mic reticulum were also present. Occasional areas showed fibrous long-spacing collagen (Luse bodies) that was closely associated with the histiocytic cells (Fig. 8). No Langerhans (Birbeck) granules or "virus-like inclusions" were identified in any cells. A few multinucleated cells were observed. A minor component of spindle-shaped fibroblasts partially surrounded by basal lamina and collagen fibrils of normal periodicity was seen; the cells had abundant intracytoplasmic granular endoplasmic reticulum. Pericapillary eosinophils, lymphocytes, and mast cells were also seen. There was no evidence of prominent pericapillary edema, reduplicated basal lamina, or endothelial cell swelling. The capillaries were unremarkable, and the endothelial cells were free of intracellular lipid despite abundant lipid droplets in surrounding xanthomatous cells.

DISCUSSION

Only a few authors have commented on DJXG. In 1965, Enzinger (9), from his experience at the Armed Forces Institute of Pathology, estimated a 5% incidence of DJXG compared with cutaneous JXG, but no specific data were presented, with the exception of one photograph of DJXG from the thigh of a 4-year-old girl. He observed that the deep form was more monotonous histologically than the cutaneous form, as was our experience. In 1972, Helwig (15) referred to unpublished data obtained in a review of 400 patents with JXG. Twenty lesions were located in either soft tissue, skeletal muscle, salivary gland, testis, stomach, periosteum, pericardium, or myocardium. Finally, in 1985 Sonoda et al. (30) described one lesion, initially diagnosed as a parotid tumor, located in the skeletal muscles of the neck of an infant. No other specific details were given.

The histological features of DJXG in our series differed from the usual concept of cutaneous JXG in that the deep lesions were circumscribed and, in general, had fewer Touton giant cells. However, this latter finding may be highly variable from lesion to lesion even in cutaneous lesions, evidenced by a third of such lesions having few to no Touton cells in one series (31). Thus, we do not believe the paucity of Touton cells to be necessarily significant.

Although this lesion is uncommon, the diagnosis of deep juvenile xanthogranuloma may be overlooked unless it is entertained in the differential diagnosis of lesions of the subcutis of young persons. This differential diagnosis is principally with deep

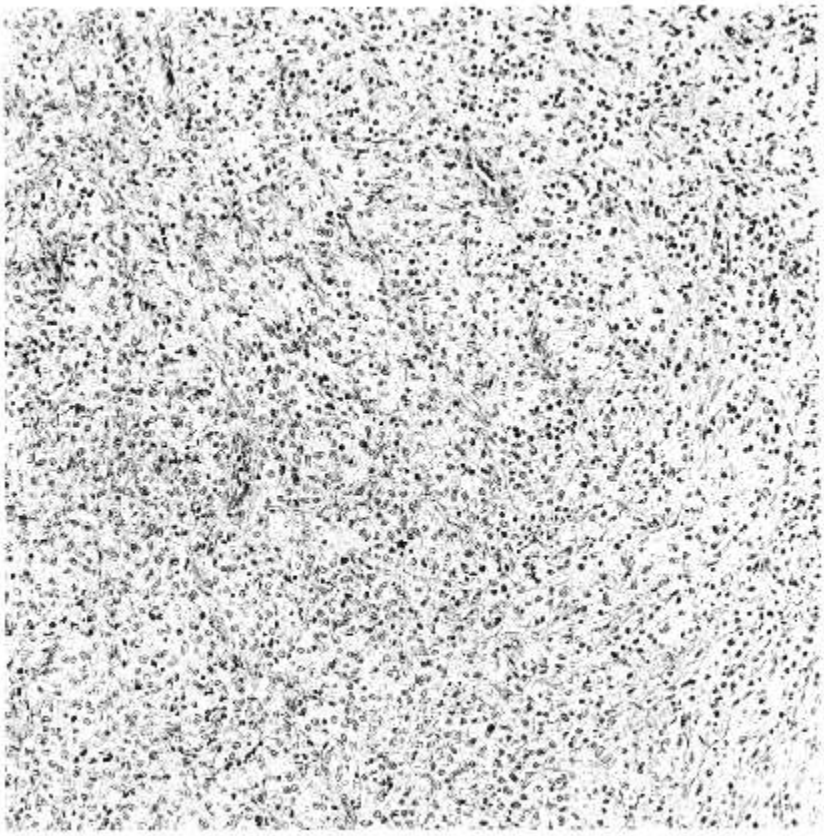


FIG. 3. Patient 2. Medium power shows a homogeneous infiltrate of epithelioid cells admixed with eosinophils.

fibrous histiocytoma and subcutaneous neurofibromas or cellular schwannomas, all of which can be differentiated on morphological grounds or with S-100 protein in the case of neural tumors.

It has been demonstrated recently that immunocytochemical markers such as α-1-antitrypsin, α-1-antichymotrypsin, and lysozyme are relatively nonspecific for so-called histiocytic lines (19,29) and, in fact, have been shown to mark a variety of disparate tissues and tumors. Thus, we view the positivity of these markers in any form of JXG as having little value in the diagnostic pathology of this lesion.

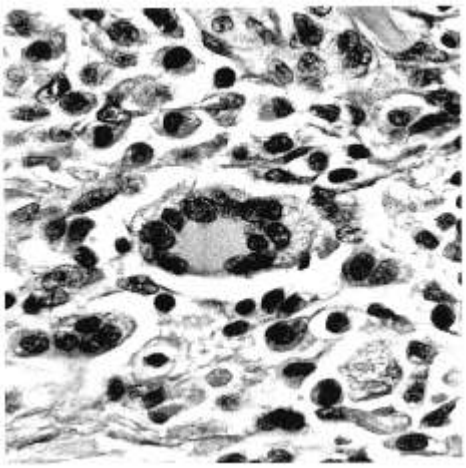


FIG. 4. Some areas showed Touton giant cells with the wreath of nuclei encircling an eosinophilic core. Several fields had to be searched in all cases before Touton cells could be found as they were relatively scarce.

However, new findings regarding JXG were seen in our small study. The diffuse positivity of control and patient lesions with the marker for HAM-56, a monoclonal antibody with specificity for monocyte-derived cells, some "fixed" tissue macrophages such as the "tingible macrophages," and interdigitating macrophages of lymph nodes as well as Kupffer cells of liver and alveolar macrophages of lung (13), suggests that the infiltrate of JXG has a similar phenotype. Additionally, the diffuse positivity of control and patient lesions with the marker for HHF-35, a monoclonal antibody with specificity for smooth, cardiac, skeletal muscle, processes such as palmar fibromatosis and myogenous tumors (32), suggests that JXG also has myofibroblastic differentiation.

Factor XIIIa, the "A" subunit of the clotting proenzyme factor XIII, is a protein that has been described in fusiform "fixed" dermal dendrocytes (dermal fibroblasts?) (5), normal mesenchyme and

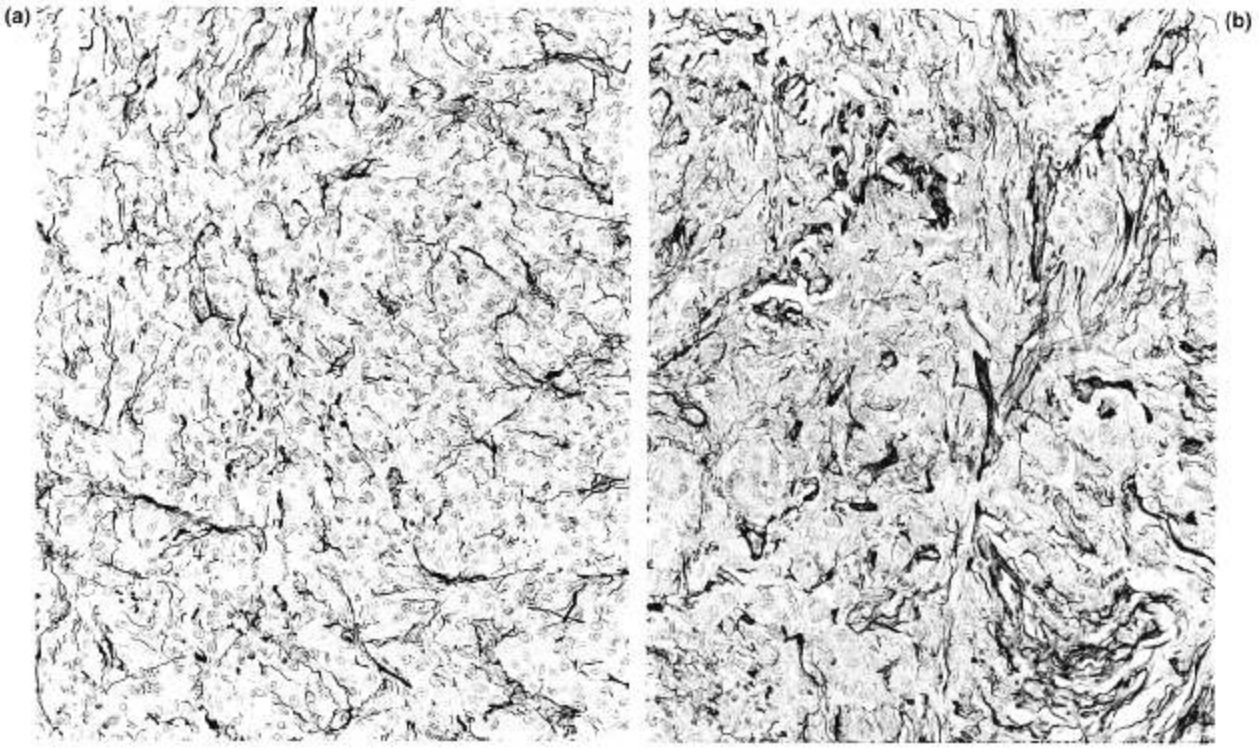


FIG. 5. Reticulin stain for the deep **(a)** and cutaneous xanthogranuloma **(b)** control. The reticulin was rich throughout the lesions; the stain isolated clusters of the infiltrate as well as outlining the vasculature.

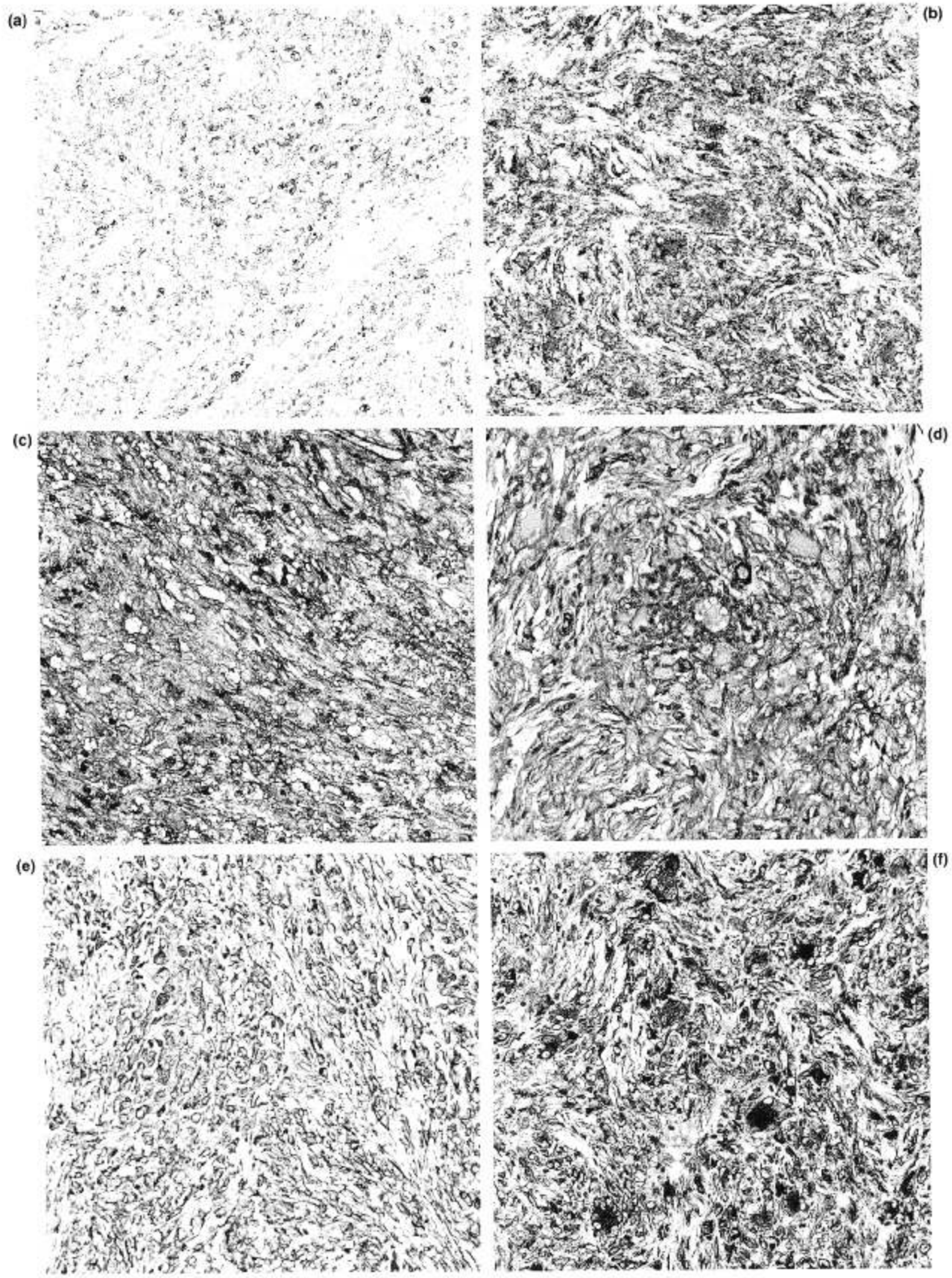
reticulum cells of lymphoid tissue (22), bone marrow-derived phagocytic cells (22), and some mesenchymal tumors. We found no positivity with the polyclonal antibody for this marker in our cases of deep and control JXG. Thus, JXG did not have the phenotypic expression of "fixed" dermal dendrocytes (fibroblasts?) in our series. Slightly different findings regarding three cases of cutaneous JXG have been reported recently by Cerio et al. (6), who described weak immunoreactivity in the epithelioid cells but found that the Touton cells were negative. We are unable to compare their results directly to ours, as their cases of JXG were not illustrated in their report; however, this issue deserves further study.

TABLE 3. *Immunohistochemical findings deep JXG and controls*

	Deep JXG		Cutaneous JXG	
Antigens	Case 1	Case 2	Control 1	Control 2
HAM 56	+++	++++	++++	++++
HHF-35	++++	++++	++++	++++
Vimentin	++++	++++	++++	++++
MAC 387	−E	−E	±P	±
Fac XIIIa	−DD	−DD	−DD	−DD
α-1-ACT	±	ND	ND	ND
α-1-AT	±	+	±	+
Lysozyme	±	−E	++	+
S-100	−D	−D	−D	−D
Fac VIIIrag	−V	−V	−V	−V

The cytoplasmic positivity within the lesional cell cytoplasm was graded + to ++++. −, no staining of the lesional cells; D, Occasional dendritic cells scattered throughout the lesion; DD, Rare positive dendrocytic cells seen peripheral to the lesion; E, Only eosinophils in the lesion were positive; ND, Not done; P, Positive cells were mainly in the peripheral portions; V, Venules within the lesion outlined.

In our hands, MAC-387, a monoclonal antibody that has been described as marking monocytes and macrophages (10), was negative in our patients and controls except for the positive cytoplasmic staining of eosinophils in lesions from our patients. Cerio et al. (6) also reported some positivity in mononuclear inflammatory cells and eosinophils in three cases of JXG. Winkelmann and Oliver (33) found diffuse positivity of xanthomatous cells in their study of four cases of subcutaneous xanthogranulomatosis studied with MAC-387. We view these findings with caution, however, in attempting to make an integrative concept from their cases to ours, as we believe their patients are clinicopathologically distinct from our patients with regard to both age and extent of disease. It follows, then, that the immunophenotypic data may be misleading if it is uncritically assumed that the lesions are identical because of some histological similarities.


(a)
(b)
(c)
(d)
(e)
(f)

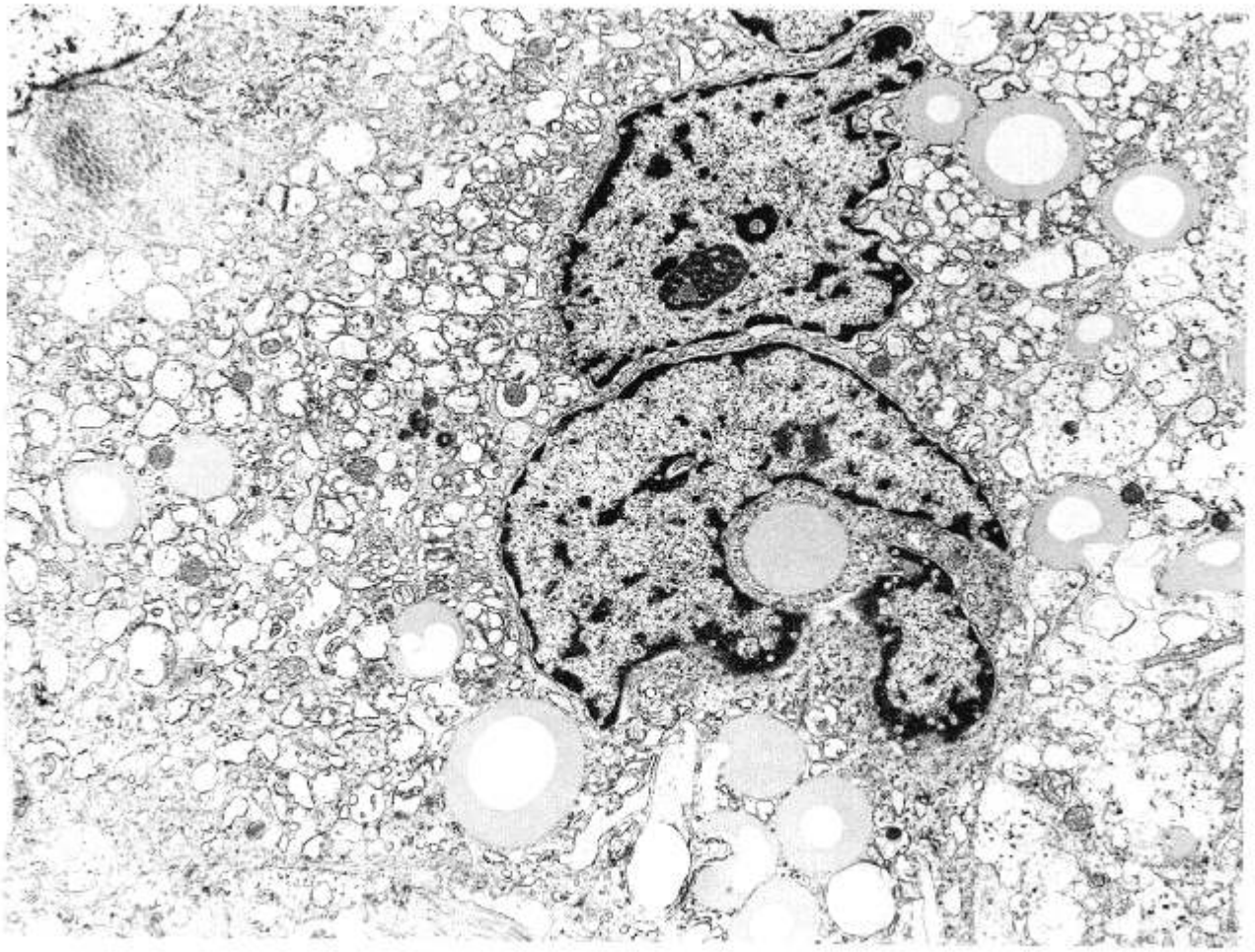


FIG. 7. Patient 2. Low-power ultrastructure shows abundant cytoplasm with numerous mitochondria, occasional lipid droplets, and irregular nuclei. No Langerhans granules or "virus-like particles" were found. (Both this and Figure 8 are from tissue fixed in formalin.)

Ultrastructurally, we believe that our case, although poorly fixed, is similar to other cases of JXG described (3,27). In the case described by Bhawan and Majno (3), lipid-laden cells, intracytoplasmic filaments, rich rough endoplasmic reticulum, and lack of basal lamina were found. They viewed their findings as consistent with myofibroblastic differentiation.

From our ultrastructural findings and positive immunostaining of HAM-56, HHF-35, and vimentin, taken in concert with the negative staining for factor XIIIa, we believe that there is support for the theory that JXG may be derived from a migrant population of macrophagic myofibroblasts. Alternatively, it is possible that JXG may be derived from a cell population *fixed* within the dermis. If the latter is proved to be true, it would be logical to conclude that the tumor cells have developed an altered phenotypic expression resembling macrophagic myofibroblasts with the concomitant loss of phenotypic markers for "fixed" dermal dendrocytes (fibroblasts?).

We conclude that the deep form of juvenile xanthogranuloma is a clinically indolent lesion with distinct histological features similar to cutaneous JXG and that our cases serve to characterize further the

FIG. 6. Deep and respective cutaneous xanthogranuloma controls for HAM-56 **(a, b)**, HHF-35 **(c, d)**, and Vimentin **(e, f)**. The cytoplasm of the mononuclear lesional cells marked with the antibodies in all cases. The nuclei were negative. The patterns for HAM-56 and vimentin were similar in that the cytoplasm of the mononuclear cells and Touton cells were positive. In contrast, the cytoplasm of the Touton cells did not mark with HHF-35.

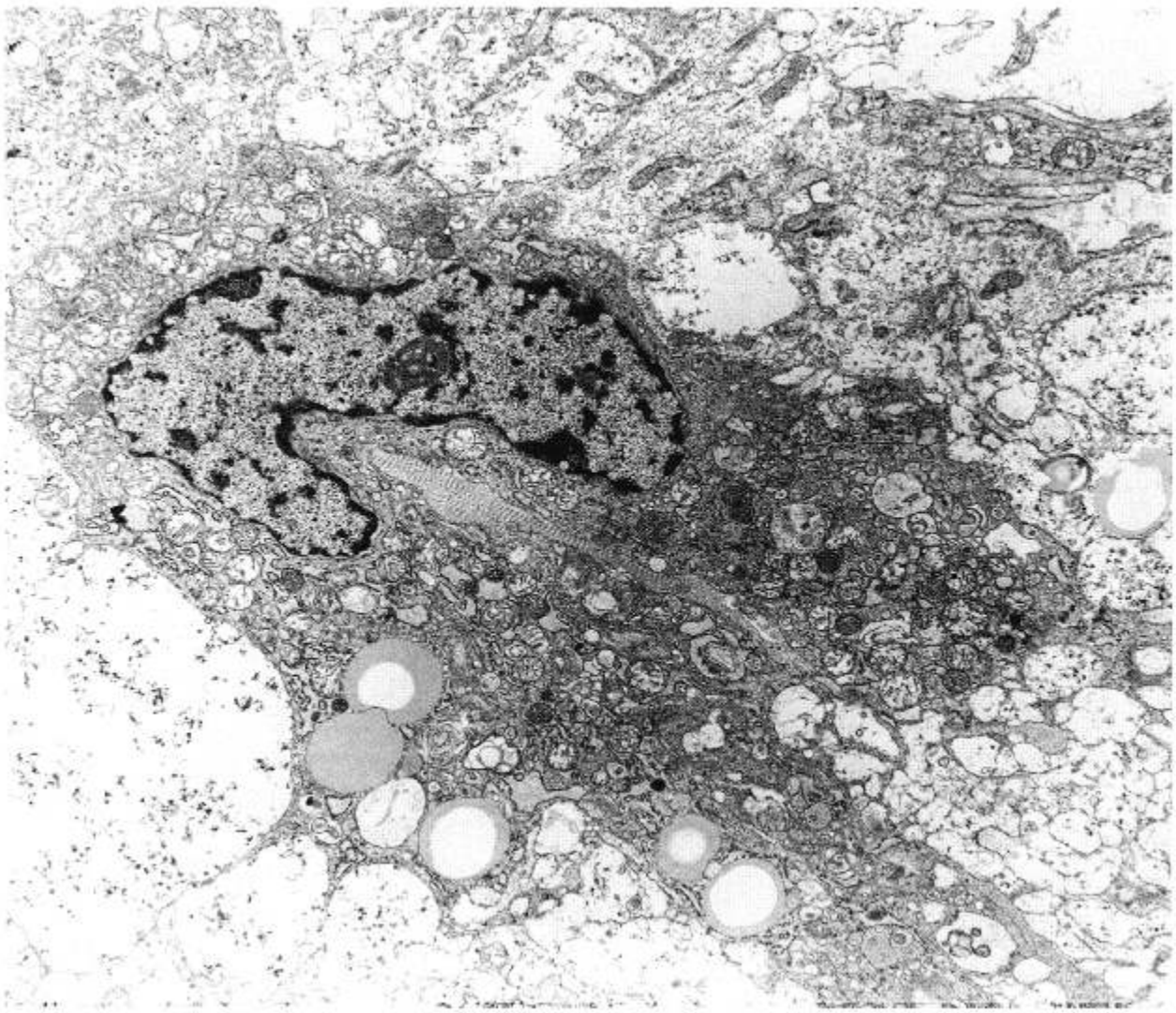


FIG. 8. Patient 2. Low-power ultrastructure shows numerous mitochondria, several lysosomes with degenerative material, and slightly dilated cisterns of smooth endoplasmic reticulum. Several lipid droplets are also seen. Fibrous long-spacing collagen indents the cytoplasm in the concave portion of the nucleus. The concave nucleus contains a single fenestrated nucleolus.

concept of JXG. Based on our findings, we believe there is evidence to support that this lesion has the phenotypic expression of macrophagic-myofibroblasts. Additional studies and a larger series of patients are indicated to substantiate further or to refute these conclusions. □

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