

# Juvenile xanthogranuloma: experience in a Children's Hospital

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## ABSTRACT

**Background.** Juvenile Xanthogranuloma (JXG), a non Langerhans CELLS histiocytosis, is a benign, self-healing disorder that affects mainly children. Extracutaneous involvement may also be present, such as ocular, liver, lung or central nervous system.

**Objectives.** 1- To identify the clinical features of patients with diagnosis of JXG as seen in the Department of Dermatology, Hospital de Pediatría "Prof. Dr. Juan P. Garrahan". 2- To describe the associated diseases and the complications of these patients. 3- To describe their outcome.

**Materials and methods.** A retrospective, observational, and longitudinal study which included all the patients with clinical and histopathological features of JXG evaluated since August 1998 to December 2006 in our Department.

**Results.** Clinical diagnosis of JXG was made in 86 patients and confirmed by biopsy in 45 of them. Forty-one patients were excluded because they didn't have histopathological confirmation. In 67% of the patients the disease appeared during the first year of life. The lesions were solitary (44%) or multiple (56%), and the most common location was the trunk (41%), followed by the head (33%) and extremities (26%). Extracutaneous involvement was present in 4 patients (9%), 3 of them with ocular manifestation with hyphema and glaucoma, and one presented multisystemic involvement.

**Conclusions.** JXG is a benign, self-healing disorder, which in the vast majority of cases is limited to the skin and requires no treatment. Nevertheless, an adequate multidisciplinary follow-up must be done to identify the extracutaneous involvement and its complications (Dermatol Argent 2010;16(4):262-267).

## Keywords:

*juvenile xanthogranuloma, non Langerhans histiocytosis, children.*

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## Introduction

The first case of juvenile xanthogranuloma (JXG) was described by Adamson (Ref 1) in 1905, who introduced the term multiple congenital xanthoma. In 1954, Helwing and Hackney (Ref 1) showed the fibrohistiocytic origin of the injuries and named them juvenile xanthogranuloma, a term with which they are known since then.

The JXG is located in the histiocytosis of non-Langerhans or type II cells, in which diseases characterized by benign proliferation of histiocytic cells are grouped.<sup>2</sup> Recently, with the advent of immunohistochemistry and ultrastructural studies, the Society of histiocytosis proposed to reclassify the histiocytosis according to the predominant cell type in 3 groups: 1) disorders resulting from dendritic cells (which include the Langerhans Cell Histiocytosis and JXG among others), 2) disorders resulting from macrophages and 3) malignant histiocytic diseases.<sup>3</sup>

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JXG is predominantly an early childhood pathology, characterized in most cases by orange-yellow papules, single or multiple, benign and self-healing (**Photo 1**). Usually, lesions are confined to the skin, although extracutaneous involvement can happen, in which case the organs most commonly affected are the eyes, CNS, lungs and liver.

Associations of JXG with myeloproliferative diseases have been described as well as with neurofibromatosis type I (NF-1), among others.<sup>4</sup>

It is histologically characterized by the presence of a dermal histiocytic infiltrate, with high lipid content and accumulation of multinucleated giant cells, known as Touton giant cells.<sup>5</sup>

In this work, we describe the clinical and histological features as well as associated diseases, the presence of complications and outcomes of all patients with clinical and histological diagnosis of JXG attended in our Department of Dermatology from August 1988 to December 2006.

## Materials and methods

We performed a retrospective, observational, longitudinal study, reviewing the clinical records of patients diagnosed with JXG belonging to the Pediatric Hospital "Prof. Dr. John P. Garrahan" between the period since its opening in 1988 until December 2006. The clinical diagnosis of the disease was confirmed in 86 patients; histopathologic examination was performed in 45 (52%) of them and the remaining 41 patients without histological confirmation were excluded from this study.

The analyzed variables were: sex, age at presentation, characteristics of lesions, involution time, histological and immunohistochemical diagnosis, associations with other diseases, differential diagnosis and presence of extracutaneous commitment and/or other complications.

To describe the variables we used the program Primer of Biostatistics version 4.02.

## Histology

All biopsies were analyzed in the Anatomical Pathology Department and stained with hematoxylin and eosin. They were classified according to their histological stage as: early JXG (onset of histiocytic proliferation), proliferative JXG (foamy cells and Touton cells are observed) or scarring JXG (when fibrosis is evident). Immunostaining was performed only on 10 (22.2%) parts due to a lack of reagents at the time of histological studies of the 35 remaining biopsies.

## Results

### Clinical Findings

The female to male rate was 1.25:1 as 25 patients (55%) were female and 20 (45%) were males. At the time of the



**PHOTO 1.** Multiple micronodular juvenile xanthogranuloma in abdomen.



**PHOTO 2.** Papular juvenile xanthogranuloma in cheek, which simulates Spitz nevus or molluscum contagiosum.

first consultation, the average age of patients was 18.2 months (standard deviation 32.4, median 11, mode 3, minimum 0.5 - maximum 180). The age appearance of the lesions covered a range from birth to 15 years old (mean 14.35 months, standard deviation 25.9, median 6, mode 1), with 67% (30) of cases before the first year of life. As reported by the parents, the evolution of the lesions until the first consultation was between 0.5 to 38 months (average of



**PHOTO 3.** Tumor with hematic crust on the scalp.



**PHOTO 4.** Ulcerated juvenile xanthogranuloma in buttock.

7.76 months, standard deviation 9.25). The persistence of injuries was only corroborated in 11 patients, among which the involution time ranged from 1 month to 4 years (mean 2.1 years).

The JXG was presented as papules (**Photo 2**) in 29 patients (65%) as a tumor in 9 (20%) one of which presented bleeding (**Photo 3**) and another one was ulcerated (**Photo 4**), as nodules in 6 (13%) and as plaques in 1 (2%) patient. The size of the lesions ranged from a few millimeters to several centimeters. The micronodular form (less than 1 cm) was observed in 18 patients (40%), the macronodular (greater than or equal to 1 cm) in 23 (51%) and no specification

of size was found in 4 patients (9%). As for the number of lesions, 56% (25) of cases presented multiple lesions and 44% (20) only one.

The trunk was the most common location (41%), followed by the head (33%) and extremities (26%); in most patients several lesions were observed at different locations simultaneously. In 2 patients (4%) their location was not recorded (**Table 1**). When patients were first evaluated, the clinical diagnosis of JXG was included in the differential diagnosis of 37 patients (82%), while in the other 8 (18%) this was not considered as probable on the initial diagnosis.

Extracutaneous involvement was clinically present in 4 patients (9%), of which 1 had multisystem involvement of lung, liver, pancreas and kidney and the remaining 3 patients presented ocular involvement.

The assessment by the Department of Ophthalmology was performed only in 18 patients (40%), which included the 3 patients referred previously. Associated diseases were found in 3 patients (7%) being NF-1, chronic myeloid leukemia and myelodysplasia.

The 41 patients (91%) with exclusive skin involvement were not treated, but rather waited for spontaneous resolution of lesions. The 3 patients (7%) with ocular involvement were treated with local corticoids and atropine. One of them evolved well, but the other 2 had to undergo surgery due to the degree of ocular involvement; one of the latter required further systemic treatment with corticoids. Both patients remain under follow-up of the ophthalmology service of our hospital because they have presented glaucoma. Regarding the patient with visceral involvement, treatment was started with systemic corticosteroids 2 mg/kg/day for a month. Due to the poor response, it was proposed to initiate an alternative treatment administrating vincristine, but unfortunately the mother refused treatment and she and her daughter failed to attend to our hospital for further controls.

### Histological findings

All patients in this study (45) showed histologic features consistent with JXG, from which: 3 (7%) were reported as early JXG and 42 (93%) as proliferative JXG (22 presented Touton cells (**Photo 5**) and 20 histiocytes with vacuolated cytoplasm, without the presence of multinucleated cells). No scarring JXG was observed. Immunostaining for CD68 was performed in 10 biopsies (22%) with a positive result in all cases (**Photo 6**).

### Discussion

The JXG is a benign tumor of histiocytic cells with predominant onset during childhood and early youth.<sup>6</sup> It belongs to the group of type II histiocytosis<sup>7</sup> and nowadays it is included in the group of histiocytosis derived from dendritic cells.<sup>3</sup> It consists of a benign and self-healing disorder, constituted



by histiocytes with graduated levels of lipids, in the absence of a metabolic disease, which affects mainly the skin and occasionally the eyes and viscera.<sup>8</sup> The etiology is still unknown, although it is presumed that histiocytic proliferation would be reactive to a stimulus yet to be determined.<sup>9</sup> It is believed that the real incidence is higher than the one described, since JXG usually occurs early in life, it is self-healing and is sometimes confused with other benign diseases.<sup>10</sup> Although several publications describe a higher incidence in males,<sup>5,10 to 14</sup> in our series of cases it was observed more frequently in females.

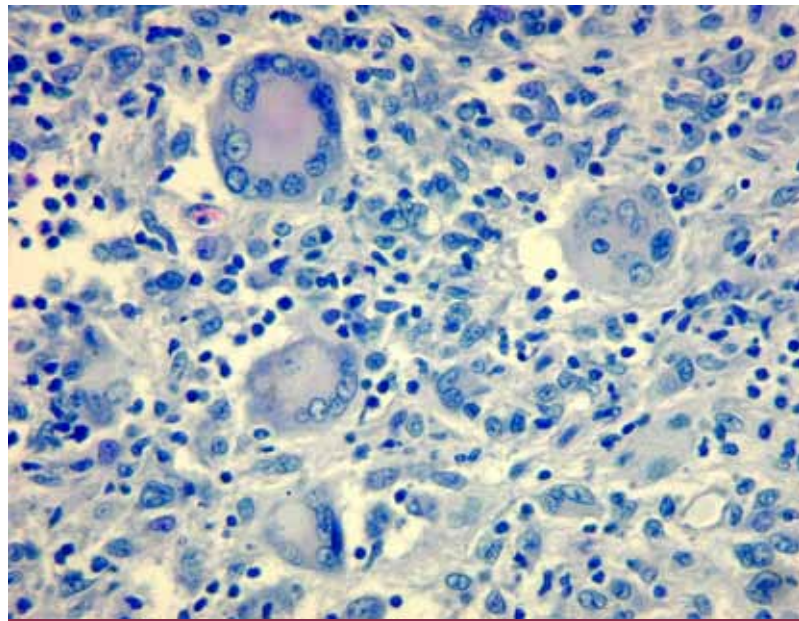
According to Sanders, JXG is 10 times more common in Caucasians,<sup>10</sup> but this information was not verified in other publications;<sup>15-17</sup> such results could not be substantiated objectively in this study, since the population of our country is predominantly white.

From a clinical standpoint, the JXG usually presents as a papule or firm nodule, neatly marked. JXG is normally asymptomatic, although sometimes depending on the location or size, it may present some symptoms. Its color ranges from pink, in the early stages, to yellow-brown; in late stages telangiectasias may develop on the surface.<sup>18</sup> The most frequent clinical manifestations observed in our study were the papular, nodular and the tumor, which is in agreement with other publications,<sup>5,10,12,13</sup> and no atypical forms such as agminated, in clusters or macular JXG, described by other authors<sup>13,19-21</sup> were observed.

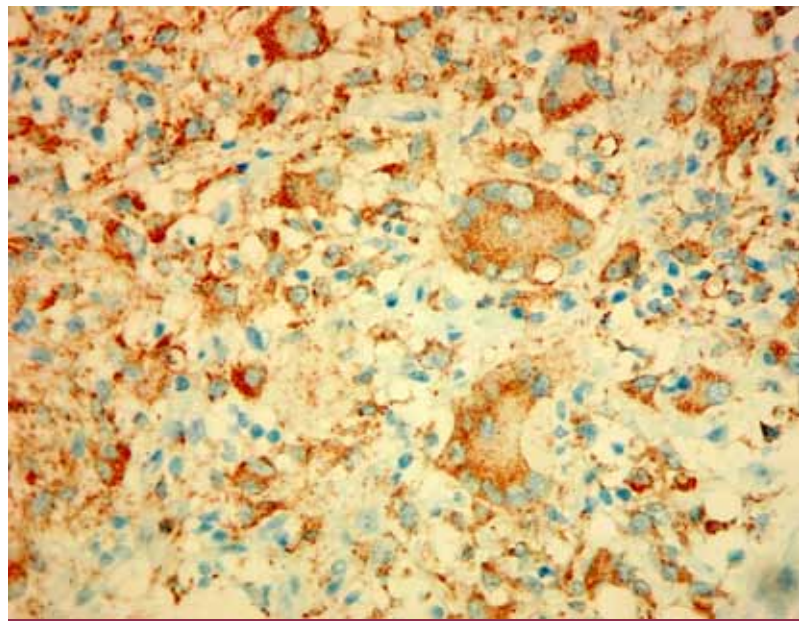
The involution of lesions starts very slowly, with decreased infiltration and central coloring. Occurs between 1 to 6 years after the appearance of lesions, and sometimes leaves residual scarring.<sup>17,22,23</sup> In our study, the involution time was only confirmed in 11 patients, and all were within 5 years. In the 34 remaining patients this information could not be collected from medical records.

Regarding the lesions onset age, in 66.7% (30) of patients JXG appeared before the first year of life, similar to that reported by other authors,<sup>6,14</sup> who describe a frequency of 40 to 75%. The age of onset did not prejudice the outcome or length of the process.<sup>24</sup>

With respect to size, Gianotti distinguished two forms of presentation: a micronodular form, more frequent, with a size smaller than 10 mm, usually of multiple lesions, and a macronodular form, with nodular lesions of less number (between 1 and 12) with sizes between 10 and 20 mm. The latter form is associated with systemic lesions of lungs, bones, kidneys, pericardium, colon, ovary and testis.<sup>9,12,25-28</sup> In our experience, we were able to certify the size of the lesions in 41 (91%) patients, of whom 18 (44%) presented the micronodular form and in 23 (56%) were of more than 1 cm large. Notably, the patient with multisystem involvement presented a macronodular form and the 3 patients with clinical intraocular commitment presented JXG of



**PHOTO 5.** Predominant histiocytic infiltrate with Touton giant cells and some eosinophils (H-E 40X).



**PHOTO 6.** Histiocytic infiltrate with Touton giant cells CD68 + (CD68 40X).

less of 1 cm, which is in agreement with other publications, in which it is described as risk factors for intraocular commitment the micronodular presentation, multiple in children of ages less than 2 years old.<sup>2,12,27</sup>

Unlike most published studies, in which it is described a major incidence of single lesions,<sup>5,10-13</sup> in our study we found that 56% (25) of patients had more than one injury.

While some authors cite the cephalic end as the most frequently affected region,<sup>5,10,12,13</sup> we found that 41% of lesions were located in the trunk, 33% on the head and 26% in

**TABLE 1. Characteristics of biopsied lesions.**

Age of onset	<1 year: 17 women, 13 men
	>1 year: 8 women, 7 men
Time of resolution	<5 years: 11
	Unspecified: 34
Clinical characteristics	Papule: 29
	Tumor: 9 (1 bloody and 1 ulcerated)
	Nodule: 6
	Plaque: 1
Number of lesions	Unique: 20
	Multiple: 25
Size	Minor 1 cm: 18
	Greater than or equal to 1 cm: 23
	Unspecified: 2
Location	Trunk: 28
	Head: 22
	Extremities: 18
	Unspecified: 2

extremities, such as published by Jassen et al.<sup>11</sup> The oral mucosal involvement is rare<sup>10, 28</sup> and none of our patients presented it.

Differential diagnoses include Spitz nevus, xanthomas and molluscs.<sup>8,9,12,16,17,22,26,29</sup> In our study, Langerhans cell histiocytosis, pyogenic granuloma, nevi, cysts and warts were, in addition to the above, other presumptive diagnoses.

In JXG with systemic involvement the most commonly affected site is the eye, followed in decreasing order by the central nervous system, lungs, liver and spleen.<sup>13</sup> In our study, the eye was too the extracutaneous organ most frequently affected; we did not find JXG in the CNS or spleen, but did find in liver, pancreas, lungs and right kidney in the only patient with multisystem involvement. Within the ocular affection, the most frequent forms of presentation are hyphema, uveitis, irritation and photophobia.<sup>13</sup> The 3 patients who showed ocular involvement, also had hyphema. The incidence of ocular involvement described in the literature ranges from 0.3 to 10%.<sup>2,3,6,7,9,10,13,27,29,30</sup> While ocular involvement in our patients was 7% (3 patients out of 45), we believe this value is less than the actual one, because 27 of them were not ophthalmologically evaluated, and it is possible that some of them had some degree of ocular involvement which was not detected.

From the histological point of view, we observe a dense infiltrate in the dermis, which contains different proportions of histiocytes, giant cells, Touton giant cells, lymphocytes, eosinophils and neutrophils. The JXG evolves into three periods: an initial proliferative period followed by a granulomatous infiltration of histiocytes, foam cells and Touton giant cells, which ends with fibrosis. The infiltrate on recent injuries consists of histiocytes with little or no lipid infiltration, lymphocytes and eosinophils. In the mature

JXG, histiocytes are vacuolated, due to lipid deposition, plus giant cells appear at this stage with a wreath of nuclei and peripheral cytoplasm also loaded with fat; these are the typical Touton giant cells. In degenerating lesions fibrosis is observed in addition.<sup>9,10,17,24,31,32</sup>

With regard to histological findings, 3 (7%) patients were consistent with early JXG, 22 (49%) presented Touton giant cells, and 20 (44%) showed a histiocytic infiltrate with vacuolated cytoplasm without multinucleated cells; no late stages of fibrosis were found. Janssen et al., in a study over 129 patients, found that 27% belonged to the early stage of JXG and 47% to the classic presentation with Touton giant cells,<sup>11</sup> which is to some extent in agreement with our study, where differences can be attributed to the time when biopsies were taken in the different series.

Kraus et al., in a study over 27 patients, showed a positive immunostaining for CD68 of 100%.<sup>33</sup> In our experience, the 10 biopsies that had the chance to immunolabel also resulted all positive.

Electron microscopy shows macrophages with complex pseudopodia. In mature lesions, macrophages contain lysosomes with variable concentration of lipids, although these are mostly located in vacuoles without a trilaminar membrane. No cells with Birbeck granules were observed.<sup>17</sup> This study was not performed in our patients.

JXG has been associated with pigmentous urticaria, Niemann-Pick disease, mellitus diabetes, myeloid leukemia and neurofibromatosis type I (NF-1). Of these, NF-1 is a disease in which significant statistic relationships have been found.<sup>18</sup> Of our patients only one of them presented a disease association to NF-1, a fact which we believe is underestimated, because within the excluded patients of the study, with clinical but not histological diagnosis of JXG, we observed a much higher association to NF-1 (4 patients with NF-1 and JXG).

The myeloproliferative disease most commonly found is a variant form of the myelomonocytic leukemia or juvenile chronic myeloid leukemia (CML) with bad evolution and fatal outcome in most of the patients.<sup>34</sup> Fortunately, this did not happen in any of the 2 patients presenting CML and myelodysplasia.

JXG treatment depends on the symptoms and complications presented. In most of our patients (91%), and as described by other authors,<sup>32, 34</sup> there were no signs of systemic involvement, which is why it was waited for a spontaneous regression without treatment. In cases in which JXG presents multisystemic involvement treatment should be started with corticosteroids and/or chemotherapy, treatment referred to our patient, but unfortunately whose mother refused to administrate. In reference to exclusive ocular involvement, according to the severity of the case, it may be suggested surgical treatment, radiotherapy, administration

of systemic or local corticosteroids.<sup>31</sup> Our 3 patients with ocular affection were treated locally with corticosteroid, of which 2 had to undergo surgery due to the degree of ocular involvement presented and one of them also had to receive systemic corticosteroids.

## Conclusions

JXG is a disease predominantly of early childhood, benign and self-healing. However, patients should be fully examined and tested in order to detect possible systemic involvement. In the event that it exists, immediate treatment is required, in order to avoid any possible future complications that may occur due to the disease.

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