CASE REPORT

Adult onset Xanthogranuloma presenting as a solitary laryngeal localization: case report and review of literature

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ABSTRACT

Juvenile Xanthogranuloma (XG) is a rare disorder that belongs to the heterogeneous group of histiocytic neoplasms, characterized by a clonal expansion of non-Langerhans cell histiocytes that share a dermal macrophage phenotype. Although the head and neck region is the most common reported site of involvement by the Juvenile Xanthogranuloma family, laryngeal localization is extremely rare. We report a unique case of Adult Onset Xanthogranuloma with subglottic localization, presenting as a solitary laryngeal mass without other systemic or cutaneous lesions. A review of the previously described cases of laryngeal Xanthogranuloma has been performed, highlighting 7 cases of Juvenile Xanthogranuloma and only 3 cases of Adult Onset Xanthogranuloma. Despite the extreme rarity of laryngeal localization of XG, this histiocytic neoplasm should be considered as a differential diagnosis for laryngeal masses causing airway obstruction, even in the absence of other concomitant manifestations.

KEYWORDS: Xanthogranuloma; Larynx; Subglottis; Histiocytic Neoplasm; Non-Langerhans; Histiocytosis

INTRODUCTION

Histiocytic neoplasms are a clinically heterogeneous group of rare disorders, which remain challenging to diagnose and treat. Adult onset Xanthogranuloma (AXG) is an uncommon histiocytic disorder that belongs to the Juvenile Xanthogranuloma (JXG) family [1], characterized by a clonal expansion of non-Langerhans cell histiocytes that share a dermal macrophage phenotype [2].

AXG commonly affects 20–40-year-old patients with no gender predilection. In adults, lesions are commonly solitary, large, and persistent, mainly affecting the skin of the head and neck region without spontaneous regression. Cutaneous lesions appear as pale yellow-tan papules, while visceral manifestations are generally nodular, of variable size and appearance. Systemic forms are rare, representing less than 5% of cases and predominantly involving lungs, long bones, peritoneum, pericardium and central nervous system [1-3].

Among tumors affecting the larynx, JXG is extremely rare. Here we report clinical and histopathological findings of a unique case of Adult onset Xanthogranuloma presenting as a solitary persistent laryngeal mass without other localizations.

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CASE REPORT

A 59-year-old male presented at our Otolaryngology department with a four-month history of hoarseness, dysphonia, cough, and occasional dysphagia for liquids, without respiratory difficulty. He had no relevant family history and no previous diseases except for arterial hypertension. He was a former smoker (52.5 packs/year). Eleven years prior, he underwent an excisional biopsy of a right vocal cord nodule with the histological diagnosis of epithelial keratosis with low grade dysplasia.

Fiberoptic laryngoscopy revealed, in the left antero-lateral wall of the subglottis, a soft and large mass of a red-brown color with a smooth surface, lined by normal mucosa. The lesion was round, well circumscribed, and occupied about 20% of the airway lumen (Figure 1). The supraglottis and glottis were normal, as was the distal trachea. Vocal fold motion was normal. The patient had no palpable neck masses, and the physical examination was otherwise normal. Routine hematological and biochemical investigations were normal.

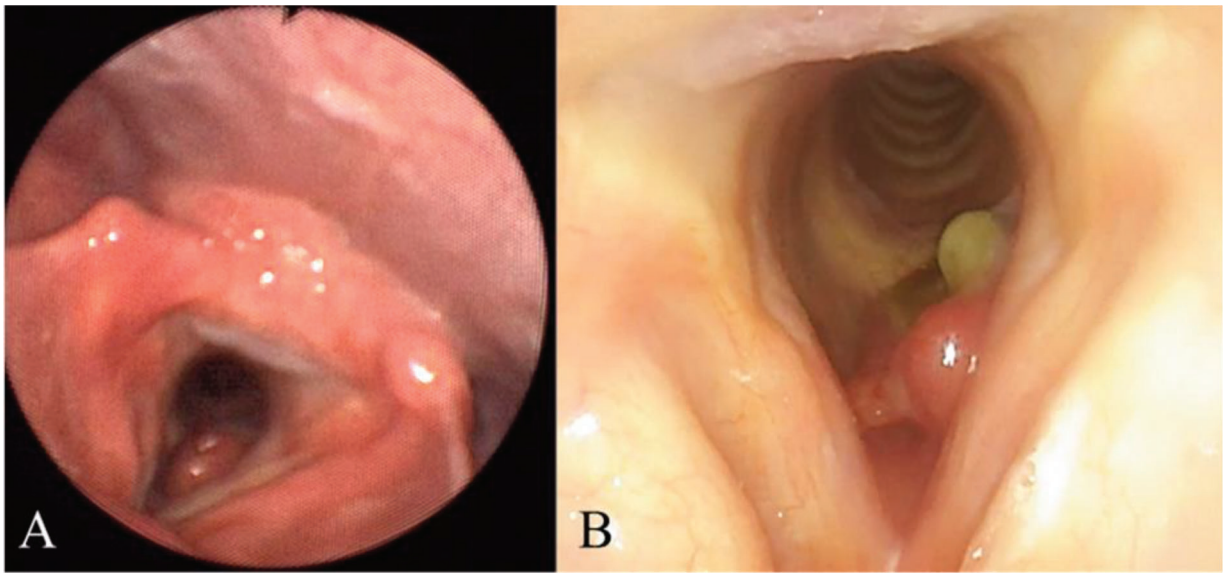

Fig. 1. Endoscopic view of the subglottic mass of the present case. A) Pre-operative examination of a mass below the true vocal cords, in the left antero-lateral wall of subglottis. B) Post-operative endoscopic view 1 year after subtotal excision showing a residue scar in the surgical field.

Subtotal resection of the subglottic mass was performed by laryngeal microsurgery under general anesthesia to determine the diagnosis and relieve the symptoms.

Microscopic examination showed biopsy specimens lined by respiratory epithelium with lympho-plasma cellular infiltrate in the lamina propria admixed to numerous histiocytes of variable size, including large sized, with frequently vacuolated cytoplasm and scattered multinucleated giant cells as well as Touton type giant cells. Regarding the nuclei of the cells, these were often large with prominent nucleolus. In addition, mitotic activity was not significant and the proliferation index, estimated using Ki67, was low (3-5%). Occasional figures of emperipolesis were observed.

A panel of immunohistochemistry was performed which confirmed the histiocytic nature of the inflammatory infiltrate, with immunohistochemical positivity for CD68/CD68r, CD163 and CD11c, although these markers were variably expressed in the large cells. S-100, CD1a and Langerin were essentially negative, with some expression found in sparse small cells in the interstitium, most likely reactive dendritic cells. Nuclear positivity for cyclin D1 was also observed. Immunohistochemistry for CD30, ALK and CKAE1-AE3 were negative.

No spores nor fungi were found (PAS, Grocott stainings) and neither Treponema pallidum (with immunohistochemistry).

All these elements put together favored a histiocytic lesion with a rich component in cells with vacuolated cytoplasm, Touton cells included, that altogether supported the diagnosis of a Xanthogranuloma (Figure 2).

Bone marrow biopsy showed a normal maturation of the three hematopoietic lines with an increase of interstitial macrophages, not correlated with what was found in the larynx.

One month after surgery the patient's dysphonia and dysphagia were relieved, with persistent occasional cough and globus sensation. Fiberoptic laryngoscopy showed normal healing of the subglottic residual mass, occupying about 5% of the airway lumen, with a scar in the surgical field and surrounded by minor perilesional grey-brown bulges.

The patient underwent PET/CT and bone marrow biopsy for workup of systemic disease, which were negative. MRI of the head and neck excluded nodal involvement and tissue infiltration. He was referred to medical oncology and hematology and no specific treatment was recommended, so a close clinical and endoscopic follow-up was performed.

He is currently monitored by the otolaryngology department and symptoms remain unvaried, with no respiratory difficulties nor other systemic manifestations. At the last follow-up, 12 months after surgery, the fiberoptic laryngoscopy shown in Figure 1 demonstrated stable subglottic residual mass and bulges, comparable to the postoperative endoscopy.

DISCUSSION

Xanthogranuloma (XG) is the prototype of a list of entities that, although differing in clinical characteristics and heterogeneity, represent the same disorder, forming the Xanthogranuloma family [3]. The classification of histiocytic disorders is in continuous evolution. In the 5th WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues [2], the most common of the histiocytic/macrophage neoplasm group is JXG, of which AXG represents a subtype.

AXG represents about 10% of all the neoplasms of the JXG family, affects subjects of each sex from the second to the fourth decade. The most frequent location is the skin of the head and neck region. Single skin lesions often occur but only occasionally can be disseminated and rarely associated with systemic manifestations as lungs, long bones, and peritoneum [1]. AXG does not regress spontaneously as frequently as seen in JXG. Association with myelodysplastic syndrome and acute lymphoblastic leukemia is described.

Treatment is based on a conservative approach, including the surgical excision with or without tracheostomy in case

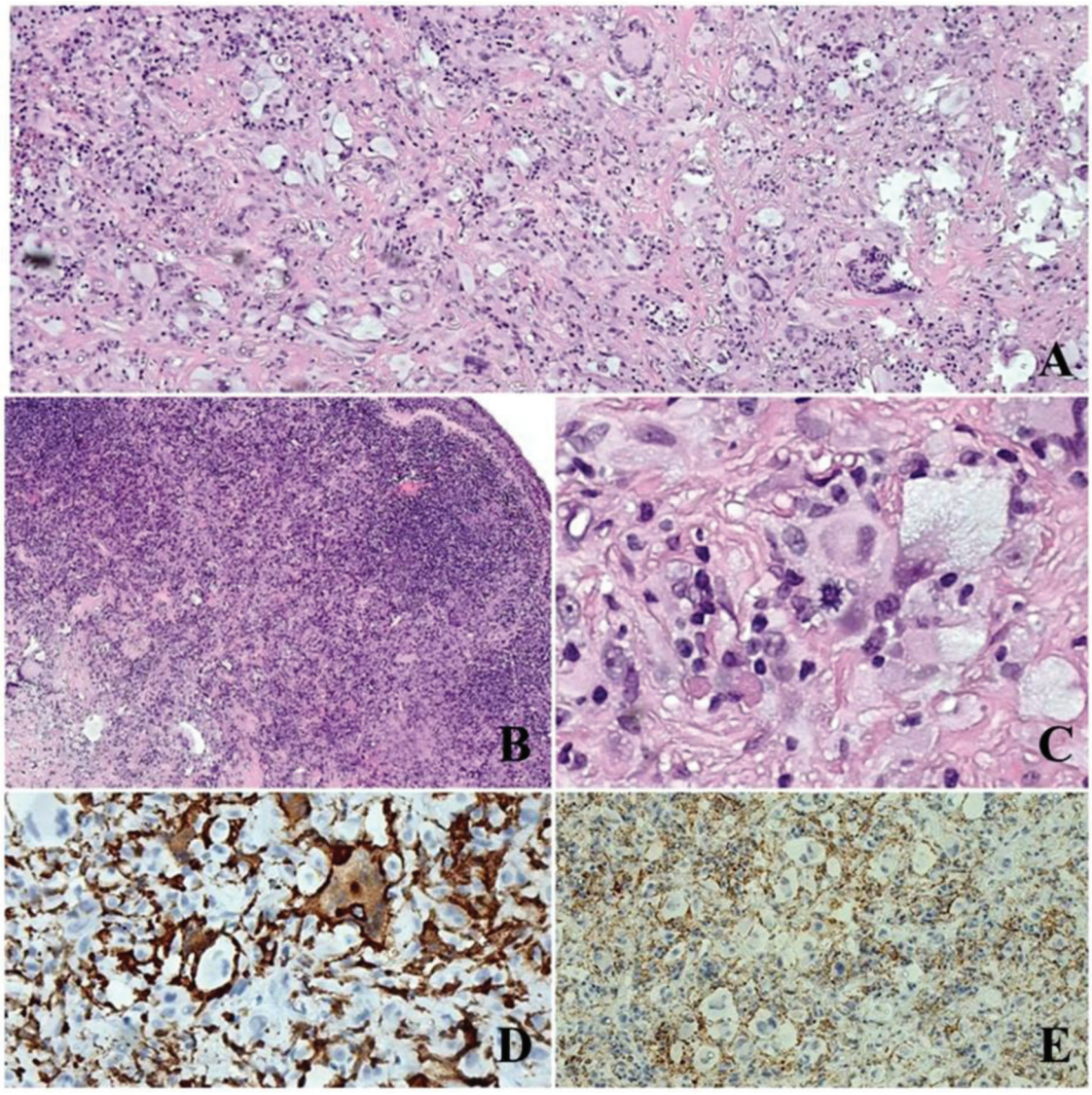

Fig. 2. Xanthogranuloma: A) H&E section (200x) showing an infiltrate composed of numerous histiocytes with clear vacuolated cytoplasm with large nuclei and prominent nucleoli associated to multinucleated Touton giant cells. Occasional figures of emperipolesis were observed. B) H&E (40x) Biopsy specimen lined by respiratory epithelium with lympho-plasma cellular infiltrate admixed to histiocytes. C) H&E (400x) detail of the picture shown in A. D-E) CD68 and CD163 expression, respectively, highlighting the histiocytic nature of these cells (IHC, anti-CD68 Ab and anti-CD163 Ab, 200x).

of respiratory impairment. Close follow-up is needed, as recurrence is possible and may require further interventions. Monitoring of the possible occurrence of hematological disorders and systemic manifestations is advised. Involvement of pericardium and central nervous system indicates an unfavorable prognosis. Chemotherapy and radiotherapy often have no impact on the disease course [1].

Diagnosis of the condition is confirmed by histological features. Histopathologically there's no difference between the XG juvenile and the adult form. Classically, cellular population is composed of large xanthomatous or foamy histiocytes and Touton giant cell that can be mixed with other cell types as epithelioid cells, spindle cells with bland ovoid indented nuclei, oncocytic histiocytes with dense eosinophilic cytoplasm and round nucleus with nucleolus. Neutrophils, plasma cells, mast cells, eosinophils and lymphocytes can often be mixed. No relevant nuclear pleomorphisms are seen. Histiocytes are positive for CD68, CD163, CD4, CD14, factor IIIa and fascin; negative for CD1a, Langerin and ALK [2,3].

Xanthogranuloma must be distinguished from other entities such as Erdheim Chester's disease, Langerhans cells histiocytosis (LCH), Rosai Dorfman's disease, ALK positive histiocytosis and epithelioid fibrous histiocytoma [2].

Erdheim Chester's disease is histologically characterized by sheets of foamy, lipid-laden histiocytes often associated with Touton giant cells, present in a variable proportion along with other inflammatory cells (small lymphocytes, plasma cells, neutrophils) and fibrosis. Histologically it can be indistinguishable from Xanthogranuloma, being therefore excluded with an appropriate clinical and radiological assessment. MAPK pathway mutations in CD163-positive macrophages, especially BRAF p.V600E, must be investigated.

Rosai Dorfman disease (RDD) usually involves lymph nodes, although extranodal disease can be observed in 43%

of cases. Histologically, RDD shows large histiocytes with round nuclei with dispersed chromatin, often prominent nucleoli, and abundant pale cytoplasm with ill-defined borders. Within the cytoplasm of these histiocytes, lymphocytes and plasma cells can be typically observed: this process is called emperipolesis, which is characteristic but not specific of Rosai Dorfman's disease. Immunophenotypically these histiocytes are S-100 positive, frequently positive to p-ERK and cyclin D1, show a variable expression for histiocytic markers as CD68 and CD163, and are not immunoreactive to CD1a and CD207/Langerin [2,3]. Although in our case occasional figures of emperipolesis were observed, most cells were S-100 negative and regarding cyclin D1 expression, which was positive, it has also been described in Xanthogranuloma [4].

Langerhans cell histiocytosis is characterized by large histiocytes with oval nuclei that display a complex morphology with nuclear folding that can be seen as nuclear grooves with dispersed chromatin and moderate to abundant eosinophilic cytoplasm. These cells express CD1a, S100, CD207/Langerin (that in immunohistochemistry is the current substitute for Birbeck granules), CD68 and can also stain for cyclin D1 and p-ERK. Multinucleated and binucleated cells, lymphocytes and eosinophils are part of the inflammatory background. Our case lacked histological morphology and positivity for CD1a and Langerin required for the diagnosis of this entity.

Although the head and neck regions are the most common reported sites of involvement by the Juvenile Xanthogranuloma family, laryngeal localization is extremely rare. A review of the English Literature revealed only 10 previously described cases of laryngeal Xanthogranuloma, of which 7 cases of JXG and only 3 cases of AXG, as shown in Table 1-2. Regarding JXG, all the 7 cases presented as solitary laryngeal localization without other manifestations. Reported symptoms were stridor, noisy breathing, and respiratory difficulty, leading to the need of tracheostomy in 2 out of the 7 cases. The subglottis was the predominant site of involvement (6/7 cases), followed by the aryepiglottic folds (2/7 cases).

In contrast to these findings concerning JXG, all the 3 previously reported cases of AXG also manifested with extralaryngeal localizations. The case described by Sampedro-Ruiz et al. [5] presented with diffuse cutaneous papules on the whole body and oropharyngeal nodules. Li et al. [6] reported a case presenting with neck and nasal masses. The case reported by Yoon D. et al. [7] manifested with multiple papules and nodules on the whole body and gingivae and showed overlapping features of AXG, Xanthoma Disseminatum and Erdheim-Chester's disease. Concerning laryngeal localization, two of these cases involved the glottis and one was not specified. The reported laryngeal symptoms were dysphonia and hoarseness and none of these patients evolved in respiratory insufficiency. Except for the case reported by Verma et al. [8], all JXG and AXG cases remained stable or showed spontaneous resolution at follow-up, as shown in Table 2.

To the best of our knowledge, the present case is the first reported AXG with subglottic localization, presenting as a solitary laryngeal mass without other systemic or cutaneous lesions. Considering the favorable prognosis, the low recurrence rate, and the mild patient's symptoms in absence of respiratory difficulty, a decision for a conservative approach with fiberoptic endoscopies scheduled every three months has been made. Currently, at 12 months follow-up the patient remains stable.

Table 1. Reported cases of Laryngeal Xanthogranuloma in the English Literature: onset, localization, and symptoms. a) Adult Onset Xanthogranuloma; b) Juvenile Xanthogranuloma. (Ns=not specified).

	Authors	Year	Sex	Age	Diagnosis	Laryngeal Onset	Localization	Other Localizations	Laryngeal Symptoms
a)	Current case	2022	M	59	AXG	Yes	Subglottis	No	Dysphonia, Dysphagia
	Sampedro-Ruiz R. et al. [5]	2021	F	57	AXG	No	Glottis	Multiple lesions on the entire body and in the oropharynx	Dysphonia
	Yoon D. et al. [7]	2019	M	31	AXG/XD/ECD	No	Ns	Multiple lesions on the entire body and on gingivae	No
	Li S. et al. [6]	2015	F	56	AXG	Yes	Vocal fold	Neck and nasal lesions	Hoarseness
b)	Verma C. et al. [8]	2022	F	4	JXG	Yes	Subglottis	No	Stridor and respiratory distress
	Kawamoto A. et al. [9]	2013	F	3	JXG	Yes	Subglottis, vocal fold	No	Stridor, hoarseness
	Wang L. M. et al. [10]	2010	M	0.8	JXG	Yes	Aryepiglottic fold	No	Stridor and sleep snoring
	Somorai M. et al. [11]	2006	M	0.4	JXG	Yes	Subglottis	No	Stridor and respiratory distress
	Sahhar H. S. et al. [12]	2003	F	1.5	JXG	Yes	Subglottis	No	Noisy breathing
	Thevasagayam M. S. et al. [13]	2000	M	3	JXG	Yes	Subglottis	No	Stridor
	Benjamin B. et al. [14]	1995	F	0.4	JXG	Yes	Subglottis, aryepiglottic folds	No	Stridor

Table 2. Reported cases of Laryngeal Xanthogranuloma in the English Literature: surgical treatment, need of tracheostomy and follow-up. a) Adult Onset Xanthogranuloma; b) Juvenile Xanthogranuloma. (Ns=not specified).

	Authors	Surgical treatment	Tracheostomy for respiratory insufficiency	Follow up time (months)	Follow up
a)	Current case	Diagnostic biopsy	No	12	Stable
	Sampedro-Ruiz R. et al. [5]	Diagnostic biopsy	No	Ns	Spontaneous resolution
	Yoon D. et al. [7]	CO2 Laser therapy	No	Ns	Stable
	Li S. et al. [6]	Excisional biopsy	No	No	No
b)	Verma C. et al. [8]	Excisional biopsy, laser and mitomycin C ablation	No	5	Recurrence without respiratory difficulty
	Kawamoto A. et al. [9]	Excisional biopsy, CO2 laser therapy	No	12	Spontaneous resolution
	Wang L. M. et al. [10]	Excisional biopsy	No	No	No
	Somorai M. et al. [11]	Diagnostic biopsy, argon laser excision	No	17	Resolution
	Sahhar H. S. et al. [12]	YAG laser	No	No	No
	Thevasagayam M. S. et al. [13]	Diagnostic biopsy	Yes	37	Spontaneous reduction, decannulation
	Benjamin B. et al. [14]	Diagnostic biopsy	Yes	11	Reduction of the lesions, decannulation

CONCLUSION

Although it is extremely rare, Xanthogranuloma should be considered as a differential diagnosis for laryngeal masses causing airway obstruction, even in the absence of other concomitant manifestations. Awareness of laryngeal involvement in Xanthogranuloma is necessary for otorhinolaryngologists and pathologists since it is important to recognize and distinguish JXG and AXG from other tumors that occur in this anatomic region.

Due to the rarity of laryngeal localizations of histiocytic neoplasms, it is difficult to determine clinicopathological differences among Xanthogranuloma and other histiocytosis in this district. Further studies are therefore warranted to compare different presentations of laryngeal localization of the various histiocytic neoplasms.

Conflict of Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report.

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