

## Hyaline-vascular Multicentric Castleman's Disease in an immunocompetent patient

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### Abstract

A previously healthy, immunocompetent 67-year-old female presented with a one-month history of general symptoms, weight loss, night fevers, and bilateral lower extremity edema. On admission she had severe anemia, acute kidney injury, and multiple lymphadenopathies. An excisional biopsy of one of the axillary lymphadenopathies confirmed hyaline-vascular Castleman's disease. This rare disease is a polyclonal lymphoproliferative disorder that affects the normal lymph node architecture. According to its location it can be divided in unicentric (localized) or multicentric disease; it can be further divided according to histopathology in hyaline-vascular or plasmatic cells variety. Clinical presentation relates more to histopathological variety than to centrality. Human herpes virus 8 is ubiquitous in this disease and, along with interleukin 6, plays an important role in pathogenesis and symptoms presentation. Surgery is the go-to treatment of localized disease, while systemic chemotherapy is the option in multicentric disease. Communication between the clinical and anatomopathological teams is crucial; lag in diagnosis can lead to futile investigations in search of other diseases and delay in treatment. (Gac Med Mex. 2015;151:604-9)  
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### Introduction

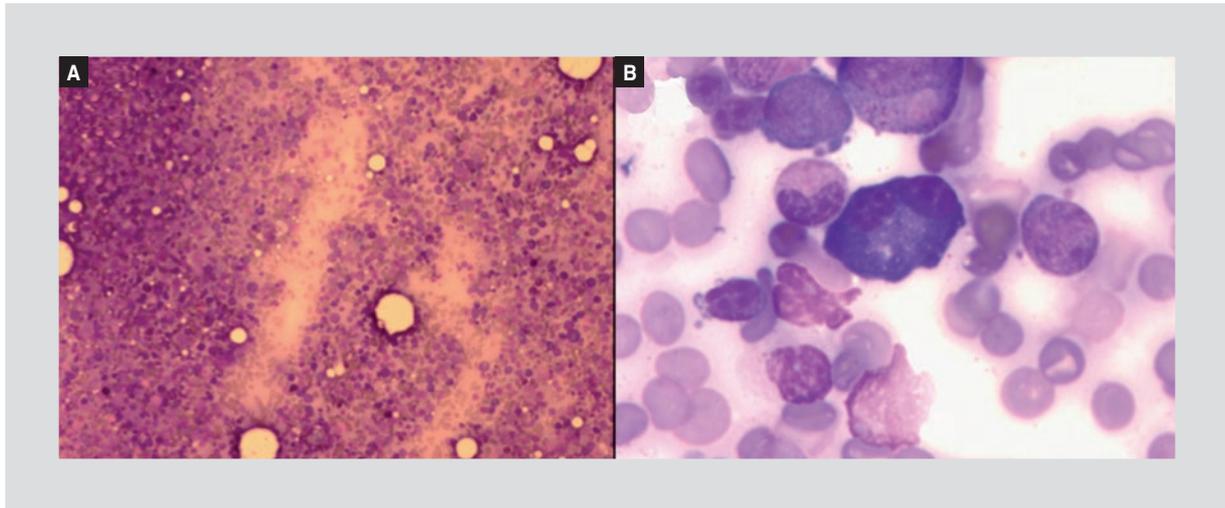
In 1954, Dr. Benjamin Castleman made the earliest description of the disease that today bears his name. Later, in 1956, he reported 13 cases of asymptomatic mediastinal masses associated with lymph node hyperplasia, which resembled thymomas<sup>1</sup>. This description prompted the study of a rare disease that affects the lymph nodes and other structures of the body's immune system. It is actually a polyclonal proliferative disorder that affects the lymph nodes' normal architecture. It can be divided according to its location in unicentric (localized)

or multicentric and according to its histologic type in hyaline-vascular or plasma cell variety. Human herpes virus-8 is ubiquitous and together with IL-6 plays an important role in the pathogenesis and clinical presentation. For this reason, it is common finding it in patients with immune system deficiencies, such as HIV-infected patients, to mention the most usual example. Here, we present the case of an immunocompetent female patient who developed the disease, which is in itself noteworthy, with a typical clinical presentation. We reinforce the illustrative nature of the case with enriching microscopy images. In spite of not being a common disease in patients with no compromise of the immune system, the

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**Figure 1.** Bone marrow with excessive cellularity for the patient's age, visualized at 10x (A). Increased plasma cells, some of them binucleated, without erythroid, granulocytic or megakaryocytic dysplasia being observed at 100x (B).

clinician should always be alert for its presence and take it into consideration within the differential diagnoses. Furthermore, the case exemplifies the importance of pathologic anatomy in the diagnostic process.

### Clinical case

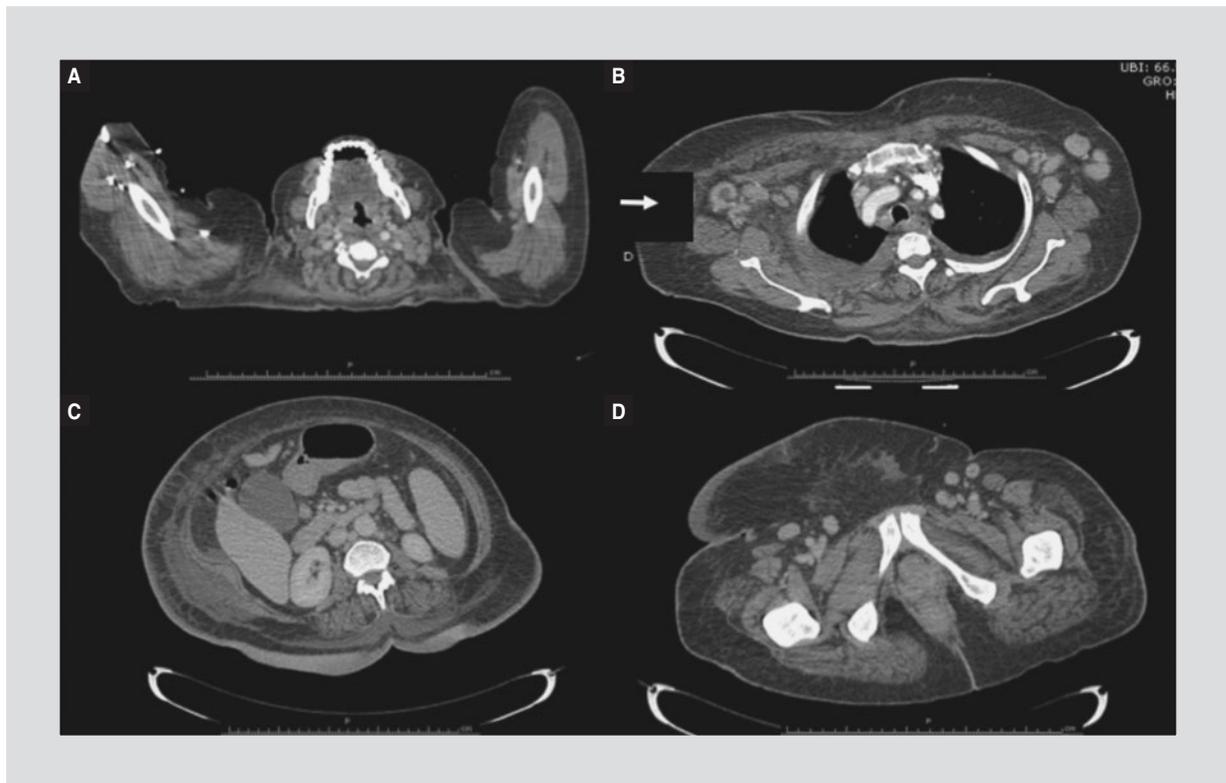
This is the case of a 67-year-old woman with a history of wood smoke exposure for 480 hours/year, previously healthy, with a 1-month history of generalized malaise, hyporexia, asthenia, adynamia, myalgias, arthralgias and non-quantified fever of nocturnal predominance, which was accompanied by nausea. Subsequently, pelvic members' edema was added to the symptoms, which made ambulation difficult. The most outstanding finding on physical examination was multiple bilateral axillary adenopathies. On admission blood count, normocytic normochromic anemia (Hb 4.8 g/dl and hematocrit 12.7%) stood out, with the remaining cell lines without abnormalities, reticulocyte index 0.2%, indicating aregenerative anemia. The rest of the studies with acute deterioration of the renal function (BUN 40.6 mg/dl, Cr 1.27 mg/dl), electrolytes and liver function tests with no irregularities (TB 0.37 mg/dl, Alb 1.8 g/dl, ALT 10 U/l, AST 15 U/l, LDH 225 U/l), ruling out hemolytic anemia. The iron profile did not show data consistent with ferropenic anemia, only elevated ferritin at 840 mg/dl, folates and B12 within normal values, ruling out iron-deficiency anemia. Plasmacytoid lymphocytes and the Rouleaux phenomenon were observed in peripheral blood smear. Hepatitis viral panel, TORCH and 4<sup>th</sup> generation ELISA for HIV were negative; none of the requested cultures developed microorganism growth.

To exclude anemia secondary to neoplasm, tumor marker tests were conducted, which turned out to be negative; recent cervical cytology and mastography showed no abnormalities. Bone marrow aspiration was performed, where marked hypoplasia of the erythroid line and 27% of plasma cells with atypical characteristics were observed (Fig. 1). Immunoglobulins showed the following values: IgG 2948, IgM 134 and IgA 461 mg/dl; IgE 390 U/ml. In view of the presence of anemia, renal lesion and immunoglobulin elevation, an approach to multiple myeloma was made by means of blood and urinary protein immunoelectrophoresis, which demonstrated no monoclonal pattern, beta-2 microglobulin levels of 4.58; skeletal x-ray failed to demonstrate lytic lesions. A computed tomography was performed, which evidenced multiple cervical, axillary, retroperitoneal and inguinal adenopathies (Fig. 2). The largest of them was found in the right axillary fossa and had a diameter larger than 2.8 cm. This lesion was biopsied for histopathological analysis, which revealed changes consistent with Castleman's disease of the hyaline-vascular variety (Fig. 3).

### Castleman's Disease. Bibliographic review

#### Association with HHV-8

HHV-8, also known as Kaposi's sarcoma-associated herpes virus (KSHV), is a human lymphotropic virus. It was first isolated in Kaposi's sarcoma tissue in 1994. It is ubiquitous in HIV-associated Castleman's disease and plays a prominent role in the pathogenesis of the disease. In HIV-seronegative patients, it is found in 40-50% of cases<sup>2,3</sup>.



**Figure 2.** Computed tomograph demonstrated multiple adenopathies located in the neck (A), axillary region, the largest of which (2.8 cm) was biopsied (B, white arrow), retroperitoneum (C) and inguinal region (D).

The virus produces several proteins involved in different cellular metabolic pathways associated with the pathogenesis of HHV-8-associated diseases. Perhaps the most important example is the viral protein homologous to IL-6 (vIL-6), which shares 25% similitude with human IL-6. The region of the virus genome with most similitude to its human counterpart is involved with the binding to the IL-6 receptor (IL-6R); however, its affinity is much lower. vIL-6 has been proposed to be able to trigger IL-6R-independent signaling pathways by glycoprotein 130 (gp130) activation or through VEGF production, which, in turn, induces IL-6 production by lymph node endothelial cells<sup>2-4</sup>.

### The role of IL-6

IL-6 is a multifunctional cytokine that induces B- and T-cells proliferation and differentiation. It is involved with the synthesis of acute phase reactant proteins, which is responsible for the development of the systemic symptoms that accompany inflammatory diseases. It plays an important role in the secretion of hepcidin, which negatively interferes with iron absorption and use<sup>5</sup>. The detection of IL-6 in lymph node germinal centers implies that its production by B-cells is related to the pathogenesis of multicentric Castleman's disease<sup>3-6</sup>.

### Location

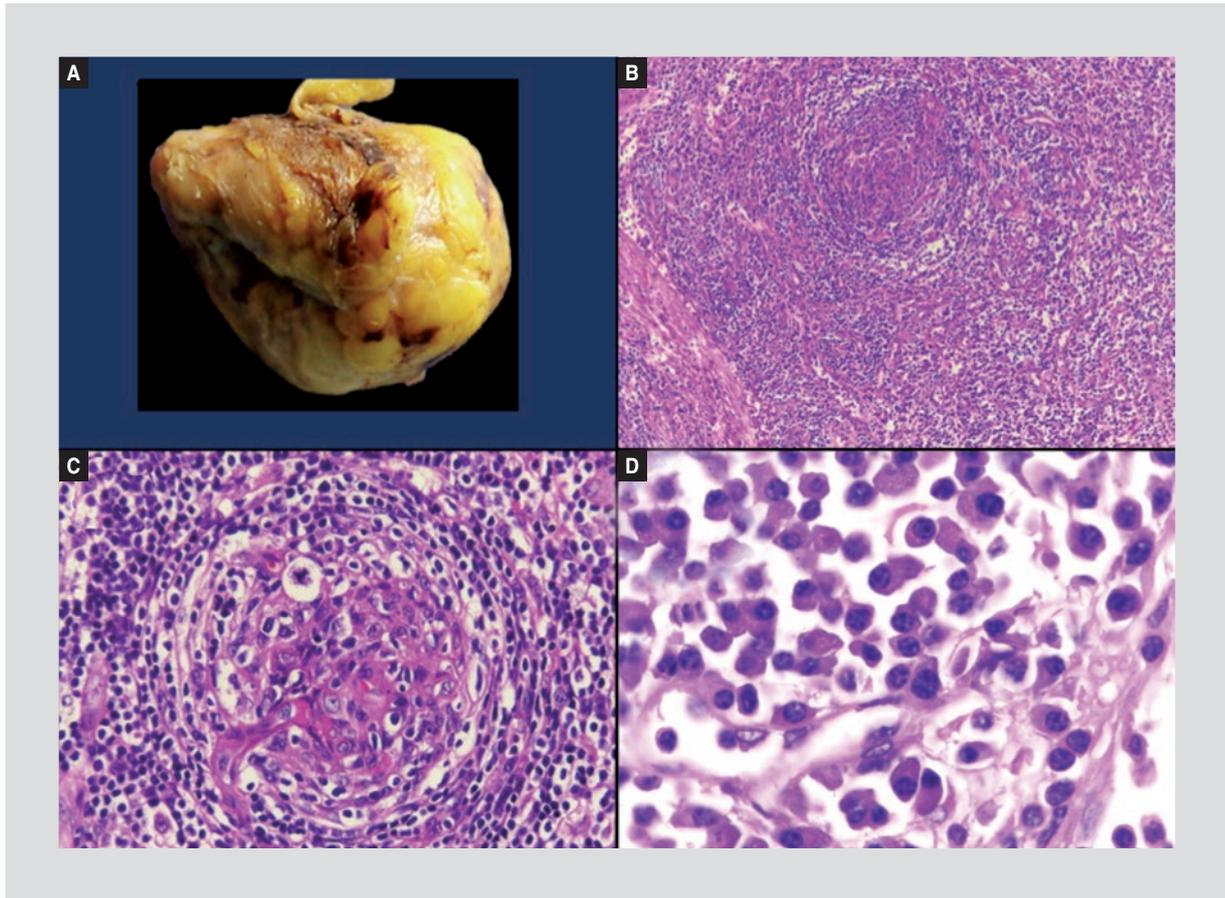
The disease can be observed at any point along the lymphatic chain, but it usually occurs at the mediastinum. The second most common site is head and neck, followed by abdomen and retroperitoneum. Other less common sites include the floor of the mouth, submandibular glands, larynx, tongue, palate region and the parapharyngeal space. Presentation in the parotid gland is an extremely rare form, with only 26 cases reported in the literature<sup>7</sup>.

### Classification

Castleman's disease occurs in different forms; historically, it has been classified according to its anatomical presentation (unicentric or multicentric) and histologic type (hyaline-vascular or plasma cell). A mixed form can occur in up to 15% of patients<sup>3</sup>.

### Clinical presentation

Symptoms are due mainly to 4 phenomena<sup>3</sup>: compressive effects by the tumor mass, cytokine activation-related systemic symptoms, fluid retention (some patients with multicentric disease show edema, ascites,



**Figure 3.** An excisional biopsy was performed of an axillary lymph node with 2.8 cm in its longest diameter (A). The lymph node architecture is modified by the presence of secondary lymphoid follicles surpassing the crust (B). The secondary lymphoid follicle shows increased thickness of blood vessels, whose wall shows hyaline changes, the so-called vascular hyaline center or lollipop image (C). In other areas, predominantly on the para-crust, an increase in the number of plasma cells is observed (D).

pericardial or pleural effusion) or due to associated diseases such as lymphoma or polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes syndrome (POEMS or Crow-Fukake syndrome). Generally, the unicentric hyaline-vascular variety causes compressive symptoms, whereas patients with the multicentric plasma cell variety present with systemic symptoms. In HIV-infected patients, the disease is usually multicentric, with plasmacytic or mixed histology. Symptoms are more severe and evolution is faster than in the immunocompetent population. It is important to highlight that the clinical presentation is correlated with the histologic subtype rather than the anatomical presentation<sup>8</sup>.

### **Anatomical classification**

The unicentric presentation is more common in children and young adults. Usually, clinical evolution is benign, and surgical resection is possible in most cases. The thoracic

location is the most common, appearing as a mediastinal ganglionic mass, which can resemble thymoma, lymphoma or neural crest-derived neoplasms, such as schwannoma or neurofibroma. The hilar form can mimic a bronchial neoplasm, while the pericardial form can be confused with a pericardial cyst. The pleural manifestation is unusual. In the gastrointestinal system, it can appear as a pancreatic tail mass, resembling a pancreatic lymphoma, adenocarcinoma or a neuroendocrine tumor<sup>7,9</sup>.

The multicentric disease presentation is more heterogeneous. It is more common at the 4<sup>th</sup> or 5<sup>th</sup> decades of life or at younger ages in HIV-infected persons. It is more associated with the plasma cell histologic variety<sup>3,9</sup>. Patients experience nocturnal fever, weight loss, general malaise, anorexia and weakness. The vast majority show multifocal lymphadenopathies, which are painful. On physical examination, hepatosplenomegaly, ascites, edema and serosal effusions (pleura, pericardium) are commonly found. Laboratory tests reveal thrombocytopenia, anemia, hypoalbuminemia and hypergammaglobulinemia. The

degree of bone marrow dysfunction can be severe and evolve to pancytopenia and organ failure.

### **Histological classification**

Castleman's disease can be classified by histologic types as well: hyaline-vascular, plasma cell, mixed and plasmablastic. The latter was recently identified.

The hyaline-vascular subtype is considered the most common form and is associated to a larger extent with unicentric disease in up to 90% of the cases. It is characterized by lymph nodes with atrophic germinal centers, occasionally lymphoid depletion, with increased thickness of the blood vessels of the germinal center that shows hyaline changes, which are concentrically displayed in the lymphoid follicle. The follicle mantle zone is well developed and shows concentric features of the onion skin-type in lymphocyte layers. All this allows for the classical lollypop image to be observed in the hyaline-vascular variant. The interfollicular areas show prominent proliferation of small vessels that commonly have thick hyalinized walls and in addition there can be hyaline material deposits.

The plasma cell variant is found only in 10% of the patients with localized disease and in up to 90% of multicentric disease cases. Histological appearance is of intense plasmocytosis in the lymphatic nodes interfollicular areas, with marked increase of capillary and postcapillary venules. Plasma cells can be identified by their "clock-face" nucleus and the presence of half moon-shaped perinuclear paleness<sup>1,3,8</sup>.

### **Imaging pattern**

The main purpose of imaging tests in Castleman's disease is to identify if it is localized or multicentric, in addition to define accessibility and resectability in cases that have to be treated with surgery<sup>4</sup>. Three tomographic patterns have been described: non-invasive isolated mass (50%), dominant infiltrating mass with associated lymphadenopathies (40%) and lymphadenopathy without presence of dominant mass (10%). Classical appearance of the hyaline-vascular variety is that of an enlarged isolated lymph node or located nodular masses with contrasted-phase homogeneous enhancement. In comparison, the plasma cell variety shows lower contrast medium uptake<sup>10</sup>.

### **Treatment**

Medical treatment of Castleman's disease depends on the presentation variety. Surgical resection is curative in the unicentric form. Radiation therapy has been

shown to improve the outcomes in those patients in whom complete resection was not possible. The use of glucocorticoids has been reported in multicentric disease, but their effects are poorly effective and short lived in HIV+ patients<sup>9,11</sup>. Some antiviral agents focusing on the prevention of HHV-8 replication have shown rates of success in the treatment of multicentric disease<sup>12,13</sup>. IL-6 inhibition with tocilizumab has been shown to produce a prolonged remission effect for more than 3 years<sup>14</sup>. Rituximab, an anti-CD20 monoclonal antibody, alone or in combination, showed significant activity in patients with and without HIV infection<sup>15</sup>.

### **Discussion**

Castleman's disease usually occurs in young adults, with no gender predominance, but it can affect persons of all ages. It is an infrequent condition, there is little information on its epidemiology and its incidence is unknown. The presence of masses in this disease commonly triggers futile investigations searching other types of tumors or other infectious or inflammatory-origin diseases, all of which were ruled out prior to the diagnosis in our case. Regardless of the histological type, the disease is characterized by lymph node architectural changes that affect all compartments (follicular, germinal and mantle). Lymph nodes appear enlarged and often show scarring areas; consequently, fine needle aspiration cytological examination is of little value, which makes excisional biopsy fundamental and necessary to establish the diagnosis<sup>1,3,8</sup>. From the clinical point of view, there is no cutoff point with regard to diameter to predict a lymph node biopsy abnormal result, although some series report that a size larger than 2 cm is suggestive of malignancy<sup>16</sup>. At the suspicion of primary hematological disease, medical, surgical and anatomical pathology team coordination is key to obtain a useful biopsy for diagnosis, since treatment with glucocorticoids and antibiotics can modify lymph node architecture and, therefore, the result<sup>16,17</sup>. In the present case, glucocorticoid administration as treatment induction was started after the bone marrow biopsy and aspiration (BMBA) and axillary lymph node biopsy. Due to the important role played by HHV-8 in the pathogenesis of the disease, it is noteworthy that the disease occurred in an immunocompetent person; although this type of cases are reported and well identified, this is not the common presentation and even more singular is the fact that it was multicentric. Another peculiarity associated with centrality is that the predominant histologic pattern was of the hyaline-vascular

**Table 1. Castleman's disease characteristics according to its centrality**

	Unicentric	Multicentric
Predominant pathologic subtype	Hyaline-vascular	Plasma cell
Systemic symptoms	Rare	Common
HIV infection	Generally negative	Generally positive
Treatment	Surgical/radiotherapy	Chemotherapy
Prognosis	Favorable	Poor

variety, an uncommon association (Table 1). There is little information published in the international literature on HIV- patients with Castleman's disease. The most representative analysis was conducted by Talat and Schulte and published in 2011<sup>18</sup>. In this study, a systematic review of 416 patients was conducted, including 384 HIV- patients (92.3%); the outcome measure was 3-year disease-free survival (DFS). The patients were classified in 4 different nosologic entities: class I, hyaline-vascular-type unicentric disease (49.5%); class II, Other (22.6%); class III, plasma cell-type multicentric disease (20.2%); and class IV, HIV+ (7.7%). In HIV- patients, outcome predictors in the univariate analysis were found to be multicentric presentation (odds ratio [OR]: 8.2, 3.4-19.4,  $p < 0.0001$ ), plasma cell subtype (OR: 6.7, 2.7-16.3,  $p < 0.0001$ ), male gender (OR: 3.1, 1.4-7.1,  $p < 0.005$ ) and age  $> 37$  years (OR: 6.4, 2.4-16.6,  $p < 0.0001$ ). Three-year DFS in class I patients was 92.5 vs. 45.7% in class III and 78% in class II patients. In HIV+ patients, 3-year DFS was 27.8% and presentation was exclusively multicentric disease. Lymphoma and Kaposi sarcoma were observed in 59.3 and 9.4% of HIV+ patients compared with 2.6 and 3.6% in HIV- subjects ( $p < 0.0001$ ). The POEMS syndrome was observed only in 7 patients (1.8%), all of them HIV-. In conclusion, we consider that the present case is an unusual presentation of an infrequent pathology such as Castleman's disease. It exemplifies the complexity of the diagnostic approach to the anemic syndrome, particularly in the absence of abnormalities in other cell lines, and the importance of close collaboration between clinical services and the pathology area. The study of adenopathies represents a true diagnostic challenge, since it is a highly common clinical finding, generally secondary to inflammatory or infectious benign processes; on the other hand, it can be, as in this case, the first manifestation of a life-threatening systemic disease.

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