



Systemic inflammatory pseudotumor, an unusual cause of fever of unknown origin mimicking a malignant lymphomatous process: case-report and review of the literature

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ABSTRACT

Background and Objectives. In recent years, a new pathologic condition – called inflammatory pseudotumor – has been occasionally described to involve many different tissues or organs. However, evidence for systemic involvement is lacking and a review of the topic potentially useful, also considering the clinical features mimicking hematologic malignancies or other clinically relevant conditions. We report a case of systemic inflammatory pseudotumor and review the literature concerning the etiopathogenesis, differential diagnosis and treatment modalities of this particular pathology.

Data Sources and Methods. The data source for this topic was MEDLINE®, searching all fields for inflammatory pseudotumor, inflammatory pseudotumor and lymph node or fever of unknown origin, pertaining to humans, published between 1970 and 1999.

Results and Conclusions. Inflammatory pseudotumor should be considered in the differential diagnosis of malignant hematologic processes and of fever of unknown origin.

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Key words: inflammatory pseudotumor, lymph nodes, liver, bone marrow

Fever of unknown origin is one of most important problems in the clinical practice of internists and hematologists. Frequently, palpable lymph nodes and spleen enlargement evoke the possibility of lymphomatous malignant processes, infection or other systemic diseases.

We describe here a case of inflammatory pseudotumor, a recently described pathologic entity, mimicking a lymphoproliferative process and presenting as fever of unknown origin. Inflammatory pseudotumor should be considered as a differential diagnosis of these clinically relevant conditions.

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Case report

We report the case of a 46-year old man admitted to hospital in June 1996 because of weakness, fever (higher than 38°C), night sweats and abdominal pain in the previous month.

On physical examination axillary and inguinal left lymphadenopathies were detected, the liver was enlarged 2 cm below the right costal margin, the spleen was palpable one cm below the left costal margin.

Table 1 shows the main laboratory parameters of the patient at admission to hospital. Serum protein electrophoresis showed a polyclonal hypergammaglobulinemia (24%); a search for fluorescent anti-nuclear antibody and rheumatoid factor was negative. Hepatosplenomegaly was confirmed by abdominal ultrasonography and CT scanning revealed mediastinal (Figure 1a) and retroperitoneal lymphadenopathies.

The differential diagnosis of fever and lymphadenopathy with hepatosplenomegaly includes several clinically relevant pathologies.

At first an infectious disease was suspected but serial bacteriologic cultures and serologic screening for specific antibodies to viruses and bacteria (hepatitis A-B-C, HIV, Epstein Barr, cytomegalovirus, *Leishmania*, *Borrelia*, *Salmonella*, *Shigella*, *Leptospira* species, *Treponema pallidum* and toxoplasmosis) did not provide diagnostic information. Following intradermal inoculation of purified protein derivative (PPD) no visible reaction was observed.

Rheumatologic disease was ruled out because of the lack of a target organ (e.g. skin, soft tissues, lung, kidney, joints) and negative specific laboratory tests.

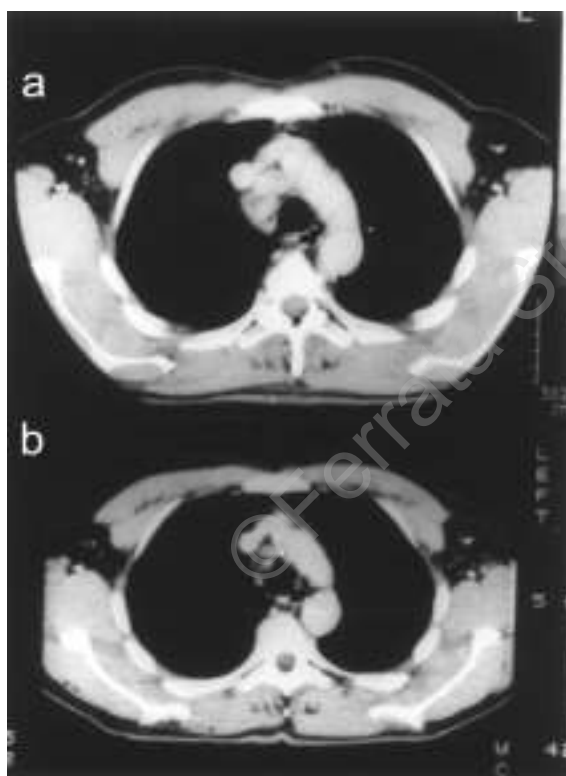
The subsequent clinical course of the patient was characterized by a spontaneous progressive improvement with remission of fever. Follow-up by CT scan also showed a spontaneous reduction in size (diameter < 5 mm) of mediastinal (Figure 1b) and retroperitoneal lymph nodes, but biochemical markers of systemic inflammation (e.g. erythrocyte sedimentation rate (ESR), fibrinogen, hypergammaglobulinemia) remained elevated.

Systemic symptoms (fever, weakness, night sweats) and lymphadenomegaly led us to suspect a malignant process such as lymphoma, although a systemic disease, such as sarcoidosis, was also considered as a more benign alternative.

Axillary lymph node biopsy resulted inadequate for

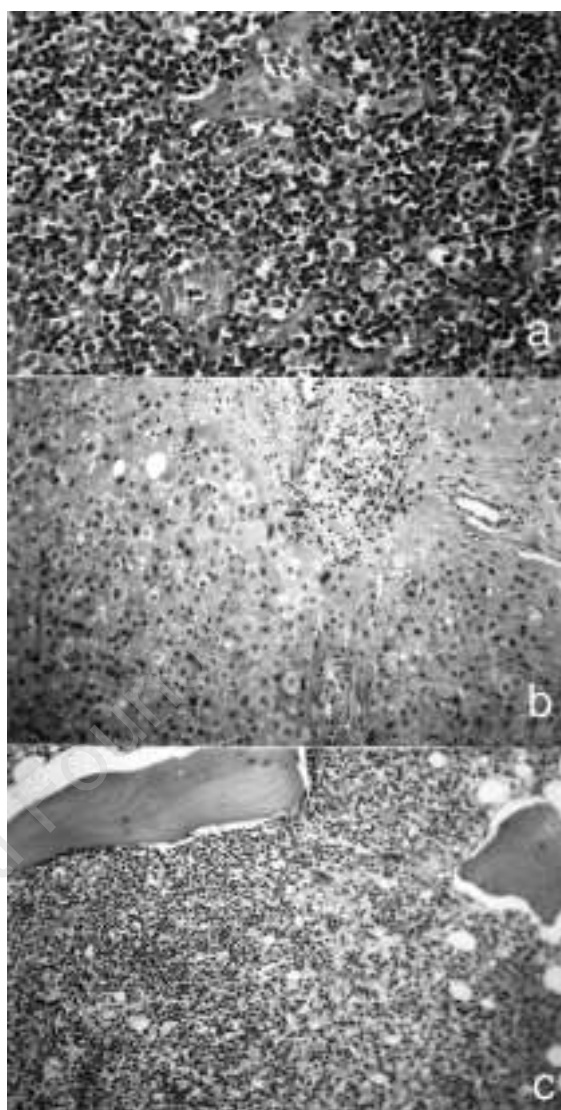
Table 1. Patient's parameters before and after steroid treatment.

Variable	On admission	6 months later
Erythrocyte sedimentation rate mm/1 st hr (n.v.<20)	117	14
Fibrinogen $\mu\text{mol/L}$ (n.v.4.4-11.7)	27.4	10.8
Hematocrit % (n.v.36-53)	32.6	39.3
Hemoglobin g/100 mL (n.v.12-17)	11.3	13.4
White blood cells $\times 10^9/\text{L}$ (n.v.4.3-10)	8.4	6.39
Bilirubin $\mu\text{mol/L}$ (n.v.3.42-18.81)	8.4	11
Alkaline phosphatase U/L (n.v. 30-130)	831	266
AST U/L (n.v. 8-50)	28	16
ALT U/L (n.v.8-45)	83	41
γGT U/L (n.v.<50)	473	174

**Figure 1. CT scan: a): mediastinal lymphadenopathies; b) spontaneous reduction in size of mediastinal lymph nodes.**

a specific diagnosis because of fat substitution. Bone marrow examination showed polymorphic lymphoid infiltration and aggregates of epithelioid cells with proliferation of reticular fibers.

Exploratory laparotomy was then performed and a lymph node of 1.6 cm in diameter adherent to the left

**Figure 2. Histopathologic findings. A: lymph node with partially conserved structure; widespread infiltration by lymphocytes associated with spindle cells and deposition of collagen can be seen (H&E, 250x); B: liver biopsy with periportal inflammatory infiltrate consisting of lymphocytes and rare plasma cells (H&E, 400x); C: bone marrow with a paratrabeular aggregate consisting of lymphocytes, plasma cells and epithelioid cells (H&E, 400x).**

renal vein was excised. Wedge biopsies of the liver were also taken. Histopathologic examination of the lymph node (Figure 2a) showed focal architectural obliteration by a polymorphous infiltrate, interspersed among the vessels, composed of spindle and inflammatory cells. The spindle cells tended to be arranged in parallel bundles within storiform patterns, and resulted to be immunohistochemically positive for vimentin; most of them were also positive for monocyte/macrophage antigen CD68, whereas others were smooth-muscle actin positive. The inflammatory component was represented by small lymphocytes, scattered immunoblasts, numerous

Table 2. Differential diagnosis of inflammatory pseudotumor.

Disease	References
Castleman's disease	Frizzera G ²⁸
Kikuchi's disease	Dorfman RF ²⁹
Kimura's disease	Hui PK ³⁰
Angiolymphoid hyperplasia	Suster S ³¹
Kaposi's sarcoma	Dorfman RF ³²
Viral, postvaccinial and drug-induced lymphadenopathies	Davis RE ¹⁷
Autoimmune diseases	Dorfman RF ³³
Kawasaki's disease	Schnitzer B ³⁴
Infectious diseases and granulomatous lymphadenitis	Dorfman RF ³³
Sinus histiocytosis and dermatopathic lymphadenopathy	Foucar E ³⁵
Malignant fibrous histiocytoma	Kyrianos M ³⁶
Dendritic and interdigitating reticulum cell sarcomas	Weiss LM ³⁷
Palisaded myofibroblastoma	Weiss SW ³⁸
Intranodal hemorrhagic spindle-cell tumor with amiantoid fibers	Suster S ³⁹
Non-Hodgkin's, peripheral T-cell and Hodgkin's lymphomas	Davis RE ¹⁷

plasma cells (polyclonal by staining for κ and λ chains), neutrophil granulocytes, rare eosinophils and rare giant cells without granulomas or foamy histiocytes. A histologic diagnosis of inflammatory pseudotumor of lymph nodes was postulated.

The liver biopsy (Figure 2b) showed a portal infiltrate of lymphocytes, plasma cells, neutrophils, focal lymphohistiocytic aggregates with some multinuclear large cells and granulomatoid foci. The picture was similar to that observed in the bone marrow specimen (Figure 2c).

The patient was treated with prednisone (50 mg a day for a week), which was tapered down and then withdrawn within six months. At present, he is symptom-free and his laboratory parameters are normal (Table 1). The clinical outcome confirmed the benign nature of this rare disease.

Discussion

Inflammatory pseudotumor (IPT) is a benign reaction which has been described in both sexes, at all age and involving many tissues: lung (over 200 cases),¹ spleen,² liver,³ gastrointestinal tract and mesentery,^{4,5} mediastinal and retroperitoneal soft tissues,⁶ pancreas,⁷ bladder,⁸ thyroid,⁹ larynx,¹⁰ meninges,¹¹ orbit,¹² heart,¹³ breast,¹⁴ epididymis,¹⁵ skin and soft tissues,¹⁶ lymph node.

However, evidence for systemic involvement of several tissues and organs is lacking. To the best of our knowledge, this is the first work in literature reporting simultaneous involvement of lymph nodes, bone marrow and liver.

In a total of 68 previously fully reported cases of inflammatory pseudotumor of lymph nodes¹⁷⁻²⁷ only two cases with inflammatory pseudotumor of lymph node had concurrent involvement of liver²⁰ or spleen.²⁴

Inflammatory pseudotumor of lymph node is a recently described benign form of lymphadenopathy, usually involving a single node but multiple nodes may be also affected at one or more sites. Some patients are completely free of symptoms, others have unexplained fever, night sweats, asthenia and weight loss, as our patient did. Intermittent symptoms are common. Perrone¹⁹ distinguishes two main patterns: a) asymptomatic patients with localized lymphadenopathy; b) symptomatic patients with several laboratory abnormalities (elevation in ESR, polyclonal hypergammaglobulinemia, mild anemia, peripheral eosinophilia, LDH increase) and evidence of one or more enlarged lymph nodes.

Diagnosis may, therefore, be difficult and often, in the absence of diagnostic signs or symptoms, an underlying malignant process is suspected. Only histologic evidence can allow a correct diagnosis. Differential histologic diagnoses include all conditions with vasculitis, fibrosis, focal necrosis, extranodal spread, partial architectural effacement and sinus or paracortical hyperplasia.¹⁷ Differential diagnosis includes many different conditions^{17, 28-39} (see also Table 2). Hodgkin's lymphoma may be particularly difficult to eliminate because of its similar mixed inflammatory infiltration and fibroblastic proliferation: however, atypical cells pathognomonic for Hodgkin's disease are lacking in IPT.

Inflammatory pseudotumor of lymph nodes primarily involves the connective tissue framework of the node (hilum, trabeculae, capsule) and show proliferation of spindle cells associated with small blood vessels and a polymorphic inflammatory cell reaction. On morphologic grounds spindle-cell types can usually be distinguished as endothelial, histiocytic or fibroblastic. Facchetti *et al.*²¹ claimed an immature histiocytic (*fibrohistiocytoid*) origin for the majority of spindle cells in IPT. Vascular changes are common but vary in degree and type (proliferation of small vessels, vasculitic changes with or without microthrombi, perivascular deposition of hyaline material, fibrinoid necrosis). Whether this vascular proliferation is of primary pathogenetic importance in inflammatory pseudotumor or a secondary feature of the process is still controversial.²¹ A recent study of 25 cases of IPT of lymph nodes distinguishes the lesions into three different groups:²⁵ stage I is characterized by the appearance of a single focus or multiple small foci containing a spindle cell proliferation admixed with a prominent inflammatory background and complete preservation of the nodal architecture; stage II by more diffuse involvement of the lymph node with a marked inflammatory response and a prominent myofibroblastic proliferation leading to subtotal effacement of the nodal architecture, often with extension of the process beyond the capsule into perinodal fat; stage III by almost complete replacement of the lymph node by diffuse sclerosis with scant residual inflammatory elements and total loss of the normal nodal architecture. A fair degree of variability in the histopathologic features of the lesions as well

as focal areas of transition between the various stages of the process suggest the existence of an evolving process.

Etiology is still unknown. IPT has been considered as either a primary immunologic lesion⁴⁰ or a fibrogenetic disorder⁴¹ or a specific reaction secondary to infectious agents,^{42,43} adjacent necrosis² or neoplasm.⁴⁴ According to Perrone *et al.*¹⁹ it is possible that many different etiologies might produce the same histologic pattern. In other words, the features of IPT might depend not on its causal agent, but rather on the modality of response to the agent. Consistent with this view, Davies *et al.*¹⁷ attributed the features of IPT to the effects of a few cytokines of inflammation, particularly interleukin 1.

The onset of disease may be acute or insidious and prolonged. Rarely, symptoms disappear spontaneously shortly after excision. This phenomenon has also been reported in similar situations in which the explanation for a possible relationship between excision and remission of clinical symptoms is equally puzzling, such as Kikuchi's necrotizing lymphadenitis.²⁰

The apparent response to non-steroidal anti-inflammatory agents, described in some patients²⁰ is difficult to assess because of the recurrent nature of the fever. Some patients have recurrent symptoms that eventually resolve; in other patients symptoms resolved after chemotherapy and/or radiation therapy had been administered for an erroneous diagnosis of malignant lymphomatous process. Steroid therapy should be the treatment of first choice. All-trans retinoic acid (ATRA) derivatives inhibit *in vitro* transformation of monocytes into neofibroblasts (collagen-producing spindle-shaped macrophages),⁴⁵ so therapy with such drugs might be of benefit.²² Finally Nishimaki *et al.*⁴⁶ observed the dramatic efficacy of cyclosporine.

On the basis of all these findings, there is growing evidence that this new pathologic entity should be included in the list of differential diagnoses of any form of lymphadenopathy with or without systemic symptoms, as well as in cases of prolonged or recurrent fever of unknown origin.

Contributions and Acknowledgments

SL and OO designed the study; SL performed the literature revision and wrote the article; RC revised the article critically; LM contributed to histopathologic descriptions. The criteria for the order in which the names of the authors appear are based on the authors' contribution to the design and execution of the study.

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