American Journal of Pathology, Vol. 137, No. 2, August 1990

Inflammatory Pseudotumor of Lymph Nodes

Immunohistochemical Evidence for Its Fibrohistiocytic Nature

Fabio Facchetti,* Chris De Wolf Peeters,* Ivo De Wever,† and Glauco Frizzera‡

From the Departments of Pathology and Surgical Oncology,† Catholic University of Leuven, Leuven, Belgium; and from the Department of Hematologic and Lymphatic Pathology,‡ Armed Forces Institute of Pathology, Washington, D.C.*

Five cases of inflammatory pseudotumor (IPT) of the lymph node were investigated by means of light microscopy and immunohistochemistry to elucidate its cellular composition. The IPT is composed of a proliferation of spindle cells, inflammatory cells, and small vessels, forming high and poor cellular areas. Many spindle cells correspond to activated histiocytes as they coexpress vimentin and macrophage-associated markers; they are intermingled with vimentin-positive fibroblasts and variable numbers of vimentin- and actin-positive myofibroblasts. This mixed-cell proliferation invades and/or destroys medium- and large-sized vessels in all cases. This study indicates that the spindle cell proliferation, identified as histiocytic and fibroblastic in nature, represents the main component of the nodal IPT. We speculate that release of cytokines by the activated histiocytes may result in the development of the complex histopathologic aspects of this inflammatory process and, if inappropriate, may represent the underlying pathogenic mechanism. (Am J Pathol 1990, 137: 281–289)

A distinctive reaction of lymph nodes resembling the inflammatory pseudotumor (IPT) of other organs recently was described as a possible cause of lymphadenopathy.[1] Histologically the process primarily involves the connective tissue framework of the node (hilum, trabeculae, capsule) and shows a proliferation of spindle cells associated with small blood vessels and a polymorphic inflammatory cell reaction. Vascular lesions, microthrombi, and/or large vessel destruction are observed in most cases. Many aspects of the disease have suggested that the histologic alterations of nodal IPT are the result of an inflammatory process in response to different etiologies.[1] However the pathogenesis and relationship of such alterations are poorly understood.

In the present study we performed a detailed immunohistochemical analysis of five cases of nodal IPT to collect data on its cellular composition. The results indicate that the fibroblastic and histiocytic proliferation is the main event in this pathologic process and suggest that cytokines released by these cell populations might be responsible for the other histopathologic findings characteristic of this disorder.

Materials and Methods

Five cases of nodal IPT were selected for this study. Two of them, cases 1 and 2, correspond to cases 5 and 6, respectively, of the previous study.[1] The clinical data on them are given in that report.

Case 3

A 23-year-old man was admitted to the hospital because of fever (higher than 39°C), night sweats, and weight loss (9 kg) in the previous 2 months. Laboratory test results were within normal limits and extensive work-up for infections was negative. On endoscopy a submucosal tumor in the gastric fundus was found. The tumor was resected and diagnosed histologically as a low-grade leiomyosarcoma. During surgical intervention, a retroperitoneal mass of 3 to 4 cm, adherent to the inferior vena cava, was noted

---

The opinions or assertions contained herein are the expressed views of the authors and are not to be construed as official or as reflecting the views of the Departments of Army, Navy, or Defense.

Accepted for publication March 8, 1990.

Address reprint requests to C. De Wolf Peeters, M.D., Department of Pathology, Laboratorium voor Histo/Cytochemie, A.Z. St. Rafaël, Catholic University of Leuven, Minderbroedersstraat 12, 3000 Leuven, Belgium.

Dr. Facchetti's current address is Department of Pathology, Spedali Civili Brescia, 25100 Brescia, Italy.

and resected. This mass showed features of nodal IPT. The postoperative course was uneventful and the patient is in good health 34 months after surgery.

Case 4

A 27-year-old man was admitted to the hospital because of fever of unknown origin and polyclonal hypergammaglobulinemia. No further clinical and laboratory anomalies were found and tests to detect infectious diseases were negative. A computed tomographic (CT) scan revealed a large retroperitoneal mass, which was surgically removed and corresponded to nodal IPT. Nineteen months after surgery the patient is in good general condition.

Case 5

The patient is a 30-year-old man who presented with fever of unknown origin and myalgia of the legs for 3 months. Physical examination showed bilateral supraclavicular lymphadenopathy. Laboratory investigations were negative, except for an elevated ESR (35 to 55), mild microcytic anemia (Hb 12.8 g/dl), with sideremia of 43 mg/dl and TIBC of 297 μg/dl, and polyclonal hypergammaglobulinemia. Tests for antinuclear antibodies and rheumatoid factor were negative, and muscle enzymes in the serum were within normal values. Extensive investigation to detect an infection etiology was negative. A right cervical lymph node biopsy was obtained and showed IPT. Fever and myalgia promptly disappeared under treatment with indomethacin. Eight months after surgery the patient is in good general condition. He still manifests left supraclavicular lymphadenopathy.

From all cases, B5 fixed, paraffin-embedded material was used for histologic and immunohistochemical investigations. From three cases, fresh frozen material was also available. On both paraffin and fresh frozen tissue sections, immunohistochemical staining was performed using an avidin-biotin complex immunoperoxidase technique (Dakopatts, Copenhagen, Denmark). The antibodies applied and their specificities are listed in Table 1. Stainings for factor-XIIIa, Mac387 and factor VIII-RA were performed after digestion of the sections with trypsin (0.1% trypsin, Sigma T 8128, in 0.1% calcium chloride, pH 7.8, at 37°C, for 10 minutes); stainings for lysozyme and alpha-1-antichymotrypsin followed digestion of the sections with brinase (0.1% brinase 50, SWE FARM Sweden, in 0.1% calcium chloride, pH 7.6, at 37°C, for 15 minutes). Staining with Ulex europaeus agglutinin-I (UEA-I) was performed applying on sections peroxidase-conjugated UEA-I for 4 hours, in a dilution of 1.2 μg/ml in phosphate-buffered saline, pH 7.2. The peroxidase reaction product was developed with a diaminobenzidine-H202 solution.

Results

In all lymph node IPTs showed morphologic abnormalities similar to those reported in detail previously.[1] Briefly, alterations were found mainly in the hilum, along the trabeculae, and in the capsule of the lymph node, extending at a variable degree into the lymph node parenchyma and the perinodal fat tissue. In these areas, pre-existing structures were replaced by a highly cellular proliferation alternating with poorly cellular scarlike tissue. The former was composed of spindle cells and admixed with inflammatory cells, including plasma cells, macrophages, lymphocytes, and neutrophils in variable proportions (Figure 1). Small vessels with flattened endothelium were regularly present; some of them showed fibrin microthrombi. The fibrous, scarlike tissue was characterized by dense collagenous stroma containing scattered spindle cells. There were fewer inflammatory cells and vessels in these areas. Large- and medium-sized veins entrapped within the IPT showed segmental destruction of their walls or luminal occlusion, either by spindle and inflammatory cells, or by fibrous tissue. Remnants of the marginal sinus and intermediate sinuses were still present, but lymphatic sinuses were no longer identifiable in the hilar region.

The lymphoid parenchyma spared by the IPT showed nonspecific reactive changes.

Immunohistochemical Findings

The relevant immunophenotyping data obtained in this study are summarized in Table 2. In the highly cellular areas, all spindle cells showed strong reactivity for vimentin (Figure 2a); many of them also were labeled by antimacrophage antibodies (Figure 2b). A few spindle cells were positive for actin (Figure 3a), and only very few of them were positive for desmin. Actin-positive spindle cells were strikingly more numerous in the fibrous scarlike areas (Figure 3b).

The inflammatory cells mainly corresponded to round or irregularly shaped macrophages (Table 2) and to plasma cells; the latter expressed polyclonal cytoplasmic immunoglobulins and were strongly positive for CD31. Lymphocytes were relatively few in number and most expressed the CD3 antigen, and equal numbers of them were of the CD4+ and CD8+ subsets. Few dendritic cells positive for S100 were noted in the IPT, whereas no spindle or dendritic cells were positive for either DRC-1, or cytokeratin 8 and 18.

Table 1. *Antibodies and Lectin Used in this Study and Their Specificities*

Antibody	Antigen distribution in human reactive lymph nodes	Type of tissue studied (°)	Source	Reference
Anti-cytoplasmic filaments antibodies				
Vimentin	Vimentin intermediate filaments; all mesenchymal cells, and macrophages.	C, P	A	2
Desmin	Desmin intermediate filaments; smooth muscle vessel walls and reticulum cells in the extrafollicular area; bundles of cells in the capsule and in the medulla.	C, P	BB	3
Actin	All six major isoforms of actin; smooth muscle vessel walls, reticulum cells in the extrafollicular area, and pericytes surrounding high endothelial venules. Bundles of cells in the capsule and in the medulla.	C	CC	3
Cytokeratin 8 and 18	Cytokeratin polypeptides no. 8 and no. 18; reticulum cells in the extrafollicular area.	C	A	4
Anti-lymphocyte reagents				
Leu4	CD3, pan T cell.	C	BD	
OKT4; Leu3a	CD4; helper/inducer T cells; macrophages.	C	O; BD	
OKT8	CD8; suppressor/cytotoxic T cells.	C	O	
Leu14	CD22; pan B cell.	C	BD	
Anti-myeloid/ macrophage reagents				
OKM1	CD11b; granulocytes, macrophages, subset of T cells.	C	O	
LeuM3	CD14; macrophages, granulocytes, interdigitating and dendritic reticulum cells; high endothelial venule endothelium.	C	BD	
SG134	CD31; granulocytes, macrophages, endothelium.	C	SG	
To5	CD35; dendritic reticulum cells, macrophages, granulocytes; some B cells.	C	D	
OKM5	CD36; platelets, macrophages, vascular endothelium.	C	O	
Lysozyme*	Macrophages, granulocytes.	P	D	5
a1-ACT*	Alpha-1-antichymotrypsin; macrophages.	P	D	6
Ferritin*	Macrophages.	P	D	7
Factor-XIIIa*	Macrophages.	P	BH	8
EBM11	22-60 kDa antigen on macrophages and interdigitating reticulum cells.	C	D	9
KP1	110 kDa antigen on macrophages.	P	OX	10
Mac387	12-26 kDa antigen on granulocytes and macrophages.	P	D	11
Anti-endothelial cell reagents				
Factor VIII-RA*	Factor VIII-related antigen; blood vessel endothelium.	C, P	D	
9 B9	Angiotensin-converting enzyme (A.C.E.); blood vessel endothelium.	C	C	12
Heca-452	200 kDa antigen on high endothelial venule endothelium, and some macrophages.	P	MA	13
UEA-I	Ulex europaeus agglutinin I, with specificity for alpha-L-fucose on blood and lymphatic vessel endothelium.	P	P	
Miscellaneous				
DRC-1	Dendritic reticulum cells.	C	D	
S100*	Interdigitating reticulum cells, dendritic reticulum cells, subset of T cells.	P	D	14
Anti-kappa*	Kappa-immunoglobulin light chain.	P	D	
Anti-lambda*	Lambda-immunoglobulin light chain.	P	D	
Anti-IgA, -IgD, -IgG, IgM.*	Alpha-, delta-, gamma-, and mu-immunoglobulin heavy chains.	P	D	

*: polyclonal antibody.
° C: cryostat sections; P: paraffin sections.
A: Amersham International, U.K.; BB: Boehringer Mannhein Biochemica, F.R.G.; CC: Chemical Credential ICN, Lisle, IL, USA; BD: Becton Dickinson, Mechelen, Belgium; O: Ortho Pharmaceutical Co., Raritan, NJ; SG: Dr. SM Goyert, Hospital for Joint Diseases, Dept. of Rheumatology, New York, NY; D: Dakopatts, Copenhagen, Denmark; BH: Behring Diagnostic, San Diego, CA: OX: Dr. DY Mason, Nuffield Department of Pathology, Oxford, U.K.; C: Institute of Experimental Cardiology, Cardiology Research Center of the USSR, Moscow, U.S.S.R.; MA: Dr. CJLM Meijer, Dept. of Pathology, Free University, Amsterdam, The Netherlands; P; Polysciences, Warrington, PA.

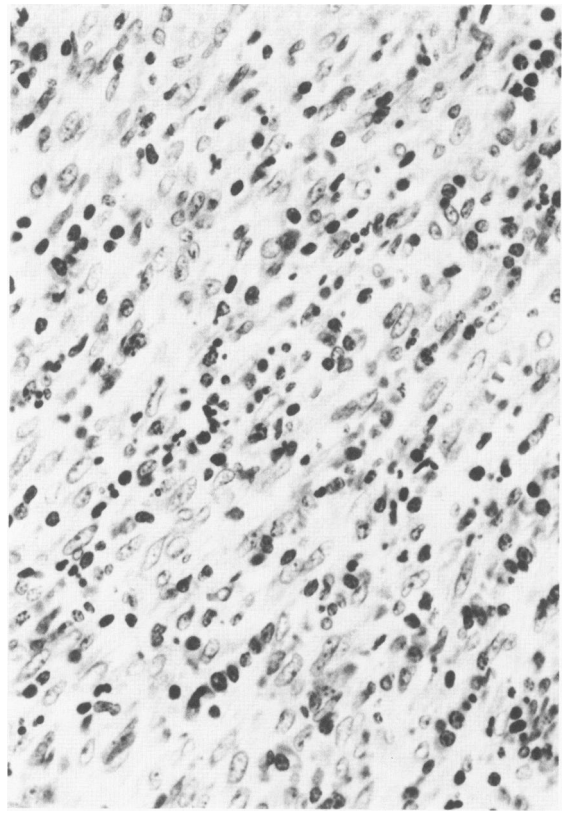

Figure 1. *Selected field of a cell-rich area of IPT, showing spindle cells admixed with inflammatory cells. Hematoxylin and eosin stain; paraffin-embedded section;* ×400.

On immunostained sections the endothelium of small vessels expressed a homogeneous phenotype throughout the IPT (Table 2). An extreme variability in the amount of vessels became obvious on these sections; furthermore the occurrence of an elaborated connecting vascular system between intra- and extranodal tissues along the IPT was visualized (Figure 4).

In addition to the vessels with signs of transmural or endoluminal involvement by IPT recognizable on hematoxylin and eosin-stained sections, immunostaining for actin and desmin revealed many remnants of muscle walls completely disrupted by the inflammatory process (Figure 5).

Lymphatic sinuses, visualized by their endothelial lining, which stained positive for vimentin and for UEA-I, were partially compressed or destroyed by IPT. No remnants of efferent lymphatics could be identified.

Discussion

Using *in situ* immunohistochemistry, we have analyzed the cellular composition of IPT of the lymph node. The process shows highly cellular areas alternating with poorly cellular, scarlike areas. The former are characterized by a spindle cell proliferation, accompanied by blood vessels, variable number of plasma cells, macrophages, and few lymphocytes. Immunophenotyping demonstrated the heterogeneity of the spindle cell component: all spindle cells were labeled for vimentin intermediate filaments, and many of them coexpressed macrophage-associated markers as well. Only scattered spindle cells were stained by antiactin antibody and a very small number by antidesmin antibody. Thus the cell-rich areas contain few spindle cells corresponding to myofibroblasts,[15–17] but are largely composed of fibroblasts and histiocytes. The latter cell population was labeled by several macrophage-associated markers, eg, CD14, KP1, Mac387, EBM11, lysozyme, ferritin, and a1-ACT, and was largely unreactive for others such as CD11b, CD31, CD35, CD36, and factor-XIIIa. These findings may indicate immaturity of these histiocytes, which might be analogous to the so-called 'fibrohistiocytoid' cells found in granulation tissue and in various chronic inflammatory conditions.[18] Alternatively, variability of expression of some antigens may result from a particular functional stage of cells of the monocyte–macrophage lineage because macrophages are lysozyme- and Mac387-positive in activated states,[5,11] whereas macrophage-derived cells can be depleted of factor-XIIIa during differentiation processes.[8,19]

The identification of most of the spindle cells as histiocytes and fibroblasts in the richly cellular areas of nodal IPT is in accordance with the observations made by Matsubara et al[20] in IPT of the lung. In contrast to Dehner's study,[21] in which myofibroblasts were found to represent the main cell component of IPT in soft tissues, myofibroblasts were absent or few in number in the cell-rich areas of IPT of the lymph node and only relatively frequent in the scarlike areas. If myofibroblasts derive from fibroblasts,[15–17,22] this discrepancy might be related to variable expression or masking of markers indicative of myofibroblastic differentiation in nodal IPT.[15,17,23]

Immunophenotyping may be helpful in distinguishing IPT from pathologic conditions of the lymph node, which are accompanied by a spindle cell proliferation. Sarcomas arising from dendritic reticulum cells and interdigitating reticulum cells have been demonstrated to retain antigenic determinants of their respective cell of origin, such as DRC-1, CD35, and S-100 protein,[24,25] none of which is found on the spindle cells of IPT. There is controversy regarding the histogenesis of the spindle cells in Kaposi's sarcoma. It was shown that these cells express endothelial antigens, eg, factor VIII-RA and UEA-I, supporting their origin from vascular[26,27] or from lymphatic endothelium;[28,29] a recent study also showed that the spindle cells in Kaposi's sarcoma express factor XIIIa, an antigen related to dermal dendrocytes.[30] None of these antigens could be demonstrated on the spindle cells in IPT.

Table 2. *Immunoreactivity of the Main Cell Components Observed in IPT*

	Spindle cells	Macrophages	Plasma cells	Blood vessel endothelium
Cytoplasmic filaments				
Vimentin	+	+/−	−	+
Desmin	−/+	−	−	−
Actin	−/+*	−	−	−
Macrophage-associated markers				
CD11b	−†	+/−	−	−
CD14	+/−	+/−	−	−
CD31	−/+	nv‡	+	+
CD35	−/+	+/−	−	−
CD36	−/+	−/+	−	+
Lysozyme	+/−	+	−	−
a1-ACT	+/−	+	−	−
Ferritin	+/−	+	−	−
Factor-XIIIa	−/+	+/−	−	−
EBM11	+/−	+	−	−
KP1	+/−	+	−	−
Mac387	+/−	+	−	−
Endothelial markers				
Factor VIII-RA	−	−	−	+/−
A.C.E.	−	−	−	−/+
Heca-452	−	−/+	−	−
UEA-I	−	−	−	+

+ All cells positive; +/− many cells positive; −/+ few cells positive; − all cells negative.
* More positive cells were found in scarlike areas.
† Many cells positive in one of three cases.
‡ Not valuable because of the intense positivity on plasma cells.

Whorled structures observed in lymph nodes with Castleman's disease were shown to be composed of spindle cells that contain factor VIII-RA–positive granules and to correspond to blood vessel endothelium.[31] Immunophenotypical data on malignant fibrous histiocytoma are contradictory.[32] Most studies, however, did not demonstrate monocyte–macrophage markers on the atypical spindle cells in this tumor,[33-35] which correlates with the origin of malignant fibrous histiocytoma from undifferentiated mesenchymal cells.[33-35] Finally intranodal hemorrhagic spindle cell tumor, a recently described mesenchymal neoplasm of inguinal nodes, can resemble IPT because of its spindle cell proliferation, which may be associated with small vessels and inflammatory cells.[36,37] Immunohistochemically and electron microscopically, this process is composed of cells that exhibit smooth muscle and myofibroblastic differentiation,[36,37] in contrast to the IPT, which is composed of a heterogeneous spindle cell population.

A proliferation of small blood vessels is another characteristic finding of nodal IPT, in analogy to IPT in other localizations.[38-40] Whether this vascular proliferation is of primary pathogenic importance in IPT[38] or a secondary feature of the process,[20,41] is controversial. Using several antiendothelial cell markers, we noted that vessels were very abundant in some areas of IPT, but entirely lacking in others. These results do not provide definitive support for either hypothesis, but they seem to indicate a secondary role for vascular proliferation in this inflammatory process. Antigens recognized by antibodies HECA-452 and anti-LeuM3 and normally present on high endothelial venule endothelium,[13,42] were not detected on the vessel endothelium within IPT. These negative results make a participation of high endothelial venules in the inflammatory process unlikely, an interpretation that is supported by the fact that IPT mainly occurs in the connective tissue framework of the lymph node, rather than in the lymphoid parenchyma.[1]

The present study confirmed the occurrence of pronounced large-vessel abnormalities (vessel-wall destruction and lumen obliteration) in IPT. Similar vascular changes have been noted in IPT occurring in other organs[39,43-45] and have raised the question as to whether an immunologic insult against structural constituents of the vessels is of primary pathogenic importance in IPT.[1,44] It should be considered, however, that these vascular abnormalities simply may indicate a peculiar destructive character of the IPT toward surrounding structures because cases of angioinvasive IPT of the lung have been shown to destroy bronchial walls as well.[39,43] That this vascular occlusion in the lymph node is the result of a gradual destruction by the IPT, rather than of primary thrombosis due to vasculitis, is supported by the absence of frank necrotic changes in the remaining lymphoid parenchyma. Observations made under pathologic[46,47] and experimental conditions,[48] in fact, have shown that vascular occlusion produces infarction of the lymphoid parenchyma. Furthermore a gradual destruction and occlusion of large vessels would also explain the formation of an elaborate

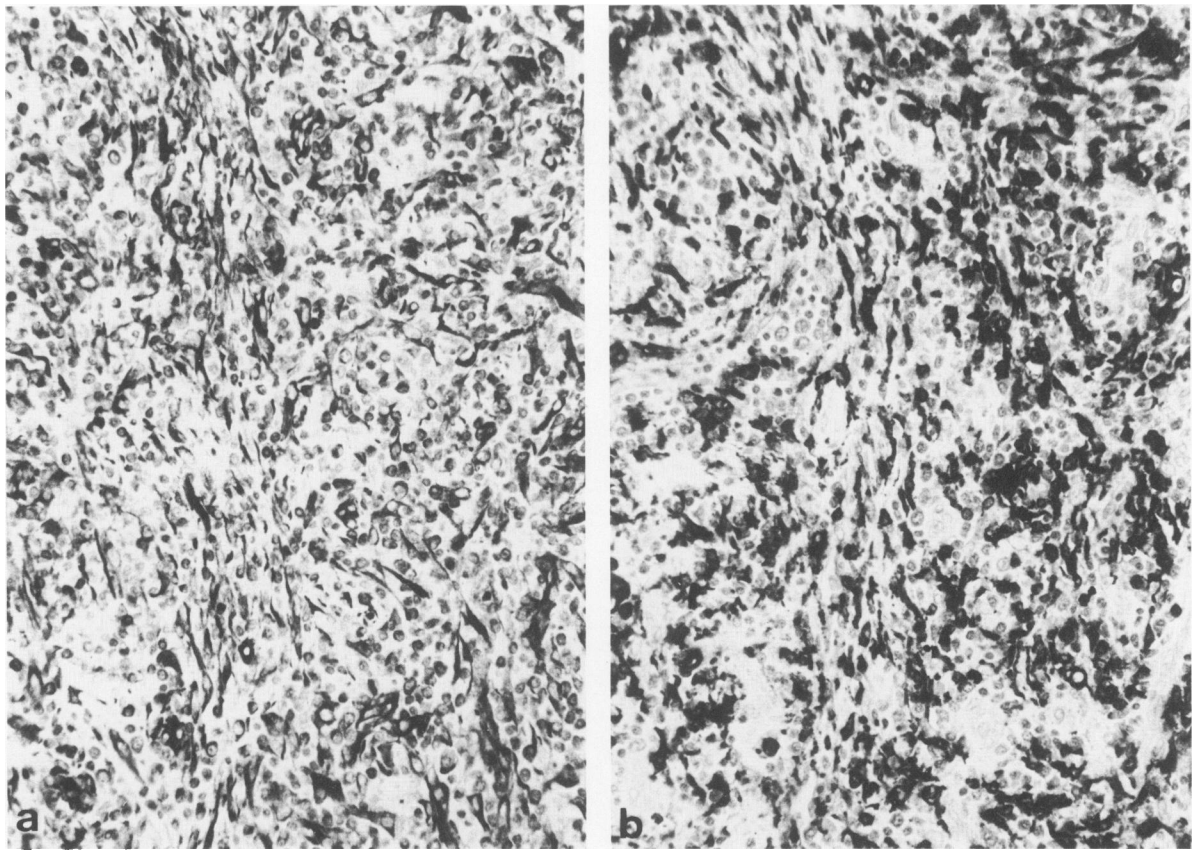

Figure 2. *Semiserial paraffin sections from a cell-rich area of IPT, stained with vimentin* (a) *and KP1* (b). *Spindle cells strongly express vimentin and many of them are KP1 positive too. In addition, vimentin and KP1 label several irregularly shaped macrophages, whereas lymphoid cells are negative for both markers. Avidin biotin complex immunoperoxidase technique for vimentin* (a) *and KP1* (b); *all* ×*400.*

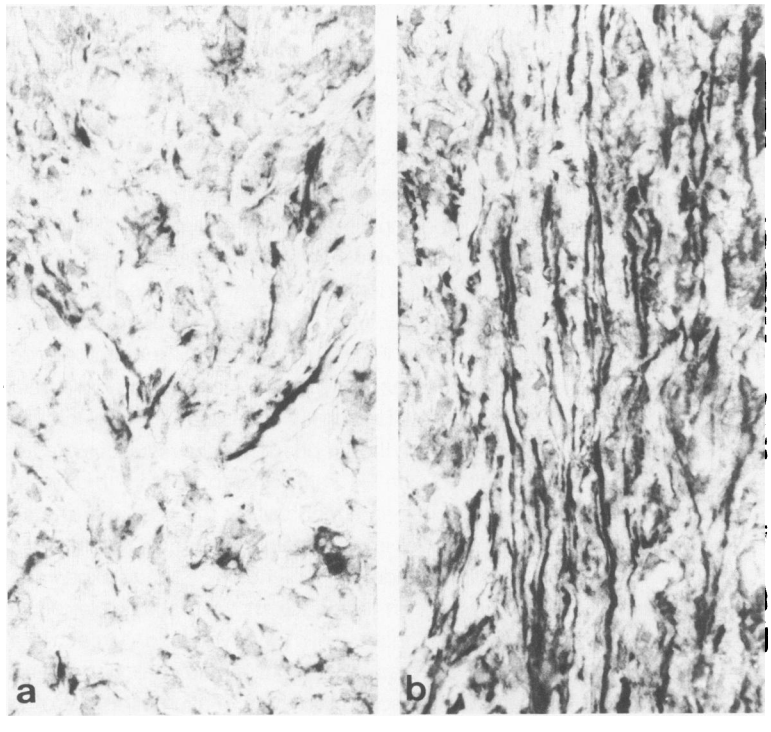

Figure 3. *Frozen sections from a highly cellular area* (a) *and from a scarlike area* (b) *of IPT, both stained for actin, and showing different numbers of actin-positive spindle cells. Avidin biotin complex immunoperoxidase technique for actin; all* ×*400.*

vascular connection between the extranodal and intranodal tissues observed in the present cases.

The etiology of nodal IPT is still unknown. Local production of mediators of inflammation can explain most features of IPT, and the activated histiocytes, the main cell component of the rich cell areas of IPT, can play a central role in this process. Interleukin-1 (IL-1) and tumor necrosis factor-alpha, two major monocyte–macrophage-derived cytokines, show overlapping biologic activities.[49] Together with other macrophage-derived factors,[50] they can be responsible for proliferation of endothelial cells,[51,52] which explains the marked vascularity of IPT, and for the formation of microthrombi,[53] frequently noted in the lumen of these vessels. The mitogenic effect of both cytokines on fibroblasts[54,55] might explain the fibroblastic cell proliferation, which can progress toward fibrosis in the scarlike areas in IPT. Finally stimulation of the fibroblasts, the endothelial cells, and even the histiocytes by locally released IL-1 can result in the secretion of interleukin-6 (IL-6) by these cells;[56,57] the latter cytokine possesses differentiation stimulatory effects on B cells[58] and, similar to what has been found in Castleman's disease, inappropriate secretion of IL-6[59] might explain the plasma cell reaction found in IPT.

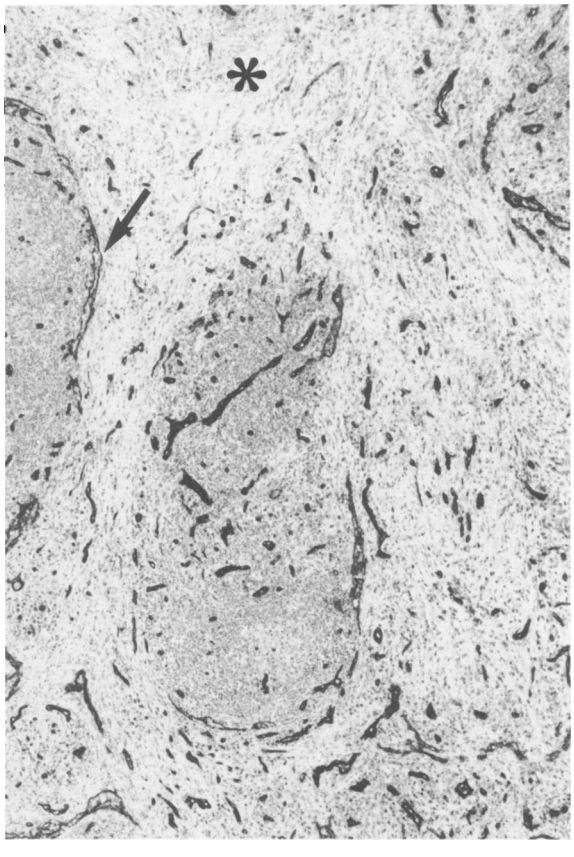

Figure 4. *Low-power view of lymph node revealing UEA-I–positive vessels connecting the extranodal (*) and the intranodal tissue, along the inflammatory pseudotumor. UEA-I–positive lymphatic sinuses (arrow), and remnants of lymphoid parenchyma are recognizable. UEA-I peroxidase-conjugated stain, paraffin-embedded section; ×160.*

Figure 5. *The wall of a large-sized vessel destroyed by the IPT. Avidin biotin immunoperoxidase technique for desmin, paraffin-embedded section; ×140.*

We were unsuccessful in demonstrating IL-6, IL-1, and tumor necrosis factor-alpha using *in situ* immunohistochemistry in our cases. Whether an abnormal secretion of such cytokines represents the basic mechanism resulting in IPT, demonstration of these cell products might require supernatant analysis from lymph node cell cultures, or a search for mRNA sequences encoding for cytokines using hybridization or polymerase chain reaction techniques.

References

1. Perrone T, De Wolf-Peeters C, Frizzera G: Inflammatory pseudotumor of lymph nodes. A distinctive pattern of nodal reaction. Am J Surg Pathol 1988, 12:351–361
2. Franke WW, Schmid E, Osborn M, Weber K: Different intermediate-sized filaments distinguished by immunofluorescence microscopy. Proc Natl Acad Sci USA 1978, 75:5034–5038
3. Toccanier-Pelte M-F, Skalli O, Kapanci Y, Gabbiani G: Characterization of stromal cells with myoid features in lymph

nodes and spleen in normal and pathologic conditions. Am J Pathol 1987, 129:109–118
4. Franke WW, Moll R: Cytoskeletal components of lymphoid organs. I. Synthesis of cytokeratins 8 and 18 and desmin in subpopulations of extrafollicular reticulum cells of human lymph nodes, tonsils, and spleen. Differentiation 1987, 36: 145–163
5. Mason DY, Taylor CR: The distribution of muramidase (lysozyme) in human tissues. J Clin Pathol 1975, 28:124–132
6. Motoi M, Stein H, Lennert K: Demonstration of lysozyme, alpha-1-antichymotrypsin, alpha-1-antitrypsin, albumin, and transferrin with the immunoperoxidase method in lymph node cells. Virchows Arch (Cell Pathol) 1980, 35:73–82
7. Mason DY, Taylor CR: Distribution of transferrin, ferritin, and lactoferrin in human tissues. J Clin Pathol 1978, 31:316–327
8. Nemes Z, Thomazy V, Adany R, Muszbek L: Identification of histiocytic reticulum cells by the immunohistochemical demonstration of Factor XIII (F-XIIIa) in human lymph nodes. J Pathol 1986, 149:121–132
9. Kelly PMA, Bliss E, Morton JA, Burns J, McGee JO'D: Monoclonal antibody EBM/11: high cellular specificity for human macrophages. J Clin Pathol 1988, 41:510–515
10. Pulford KAF, Rigney E, Jones E, Stross P, Mickelm K, Gatter KC, Mason DY: KP1- A monoclonal antibody detecting a new monocyte/macrophage associated antigen in routinely processed tissue sections. J Clin Pathol 1989, 42:414–421
11. Flavell DJ, Jones DB, Wright DH: Identification of tissue histiocytes on paraffin sections by a new monoclonal antibody. J Histochem Cytochem 1987, 35:1217–1226
12. Danilov SM, Faerman AI, Printseva OY, Martynov AV, Sakharov IY, Trakht IN: Immunohistochemical study of angiotensin-converting enzyme in human tissues using monoclonal antibodies. Histochemistry 1987, 87:487–490
13. Duijvestijn AM, Horst E, Pals St, Rouse BN, Steere AC, Picker LJ, Meijer CJLM, Butcher EC: High endothelial differentiation in human lymphoid and inflammatory tissues defined by monoclonal antibody Heca-452. Am J Pathol 1988, 130:147–155
14. Takahashi K, Isobe T, Ohtsuki Y, Sanabe H, Takeda I, Agaki I: Immunohistochemical localization and distribution of S-100 protein in the human lymphoreticular system. Am J Pathol 1984, 116:497–503
15. Gabbiani G, Ryan GB, Lamelin J-P, Vassalli P, Majino G, Bouvier CA, Cruchaud A, Lüscher EF: Human smooth muscle autoantibody. Its identification as antiactin antibody and a study of its binding to "nonmuscular" cells. Am J Pathol 1973, 72:473–484
16. Schürch W, Seemayer TA, Lagace R, Gabbiani G: The intermediate filament cytoscheleton of myofibroblasts: An immunofluorescence and ultrastructural study. Virchows Arch (Pathol Anat) 1984, 403:323–336
17. Eddy RJ, Petro JA, Tomasek JJ: Evidence for the nonmuscle nature of the "myofibroblast" of granulation tissue and hypertrophic scar. Am J Pathol 1988, 130:252–260
18. Imai Y, Yamakawa M, Sato T: Morphological, enzyme histochemical and immunohistochemical studies of granulation tissue. Proposal of "Fibrohistiocytoid cells". J Leukocyte Biol 1987, 42:396(Abstr)
19. Cerio R, Spaull J, Wilson Jones E: Identification of Factor XIIIa in cutaneous tissue. Histopathology 1988, 13:362–364
20. Matsubara O, Tan-Lui NS, Kenney RM, Mark EJ: Inflammatory pseudotumors of the lung: Progression from organizing pneumonia to fibrous histiocytoma or to plasma cell granuloma in 32 cases. Hum Pathol 1988, 19:807–814
21. Dehner LP: Extrapulmonary inflammatory myofibroblastic tumor: The inflammatory pseudotumor as another expression of the fibrohistiocytic complex. Lab Invest 1986, 54:15(Abstr)
22. Gabbiani G, Hirschel BJ, Ryan GB, Statkov PR, Majino G: Granulation tissue as a contractile organ. A study of structure and function. J Exp Med 1972, 135:719–734
23. Skalli O, Schürch W, Seemayer T, Lagacè R, Montandon D, Pittet B, Gabbiani G: Myofibroblasts from diverse pathologic settings are heterogeneous in their content of actin isoforms and intermediate filament proteins. Lab Invest 1989, 60: 275–285
24. Monda L, Warnke R, Rosai J: A primary lymph node malignancy with features suggestive of dendritic reticulum cell differentiation. A report of 4 cases. Am J Pathol 1986, 122: 562–572
25. Van den Oord JJ, De Wolf-Peeters C, De Vos R, Thomas J, Desmet VJ: Sarcoma arising from interdigitating reticulum cells: Report of a case, studied with light and electron microscopy, and enzyme- and immunohistochemistry. Histopathology 1986, 10:509–523
26. Rutgers JL, Wierczorek R, Bonetti F, Kaplan KL, Posnett DN, Friedman-Kien AE, Knowles DM: The expression of endothelial cell surface antigens by AIDS-associated Kaposi's sarcoma. Evidence for a vascular endothelial cell origin. Am J Pathol 1986, 122:493–499
27. Facchetti F, Lucini L, Gavazzoni R, Callea F: Immunomorphological analysis of the role of blood vessel endothelium in the morphogenesis of cutaneous Kaposi's sarcoma: A study of 57 cases. Histopathology 1988, 12:581–593
28. Beckstead JH, Wood GS, Fletcher V: Evidence for the origin of Kaposi's sarcoma from lymphatic endothelium. Am J Pathol 1985, 119:294–300
29. Russel Jones R, Spaull J, Spry C, Wilson Jones E: Histogenesis of Kaposi's sarcoma in patients with and without acquired immune deficiency syndrome (AIDS). J Clin Pathol 1986, 39:742–749
30. Nickoloff BJ, Griffiths CEM: The spindle-shaped cells in cutaneous Kaposi's sarcoma. Histologic simulators include Factor XIIIa dermal dendrocytes. Am J Pathol 1989, 135:793–800
31. Nagai K, Sato I, Shimoyama N: Pathohistological and immunohistochemical studies on Castleman's disease of the lymph node. Virchows Arch (Pathol Anat) 1986, 409:287–297
32. Fletcher CDM: Malignant fibrous histiocytoma? Histopathology 1987, 11:433–437
33. Lawson CW, Fisher C, Gatter KC: An immunohistochemical study of differentiation in malignant fibrous histiocytoma. Histopathology 1987, 11:375–383
34. Roholl PJM, Kleyne J, Van Unnik JAM: Characterization of tumor cells in malignant fibrous histiocytomas and other soft-

tissue tumors, in comparison with malignant histiocytes. Am J Pathol 1985, 121:269–274

35. Wood GS, Beckstead JH, Turner RR, Hendrickson MR, Kempson RL, Warnke RA: Malignant fibrous histiocytoma tumor cells resemble fibroblasts. Am J Surg Pathol 1986, 10: 323–335
36. Suster S, Rosai J: Intranodal hemorrhagic spindle-cell tumor with "amianthoid" fibers. Report of six cases of a distinctive mesenchymal neoplasm of the inguinal region that simulates Kaposi's sarcoma. Am J Surg Pathol 1989, 13:347–357
37. Weiss SW, Gnepp DR, Bratthauer GL: Palisaded myofibroblastoma. A benign mesenchymal tumor of lymph node. Am J Surg Pathol 1989, 13:341–346
38. Spencer H: The pulmonary plasma cell/histiocytoma complex. Histopathology 1984, 8:903–916
39. Warter A, Satge D, Roeslin N: Angioinvasive plasma cell granulomas of the lung. Cancer 1987, 59:435–443
40. Dehner LP, Kaye V, Levitt C, Askin FB: Cellular inflammatory pseudotumor in young individuals: A lesion distinguishable from fibrous histiocytoma or myosarcoma? Lab Invest 1981, 44:14(Abstr)
41. Antony PP, Telesinghe PU: Inflammatory pseudotumor of the liver. J Clin Pathol 1986, 39:761–768
42. Turner RR, Beckstead JH, Warnke RA, Wood GS: Endothelial cell phenotypic diversity. In situ demonstration of immunologic and enzymatic heterogeneity that correlates with specific morphologic subtypes. Am J Clin Pathol 1987, 87: 569–575
43. Bahadori M, Liebow AA: Plasma cell granulomas of the lung. Cancer 1973, 31:191–208
44. Someren A: "Inflammatory pseudotumor" of liver with occlusive phlebitis. Am J Clin Pathol 1978, 69:176–181
45. Chen KTK: Inflammatory pseudotumor of the liver. Hum Pathol 1984, 15:694–696
46. Watts JC, Sebek BA, McHenry MC, Ellestyn CB: Idiopathic infarction of intraabdominal lymph nodes. A cause of fever of unknown origin. Am J Clin Pathol 1980, 74:687–690
47. Maurer R, Schmid U, Davies JD, Mahy NJ, Stansfeld AG, Lukes RJ: Lymphnode infarction and malygnant lymphoma: A multicentre survey of European, English and American cases. Histopathology 1986, 10:571–588
48. Osogoe B, Courtice FC: The effects of occlusion of the blood supply to the popliteal lymph node of the rabbit on the cell and protein content of the lymph and on the histology of the node. Aust J Exp Biol Med Sci 1968, 46:515–524
49. Le J, Vilcek J: Biology of Disease. Tumor necrosis factor and Interleukin 1: Cytokines with multiple overlapping biological activities. Lab Invest 1987, 56:234–248
50. Polverini PJ, Cotran RS, Gimbrone MA Jr, Unanue ER: Activated macrophages induce vascular proliferation. Nature 1977, 269:804–806
51. Ooi BS, Mac Carthy EP, Hsu A, Ooi YM: Human mononuclear cell modulation of endothelial cell proliferation. J Lab Clin Med 1983, 102:428–433
52. Leibovich SJ, Polverini PJ, Shepard HM, Wiseman DM, Shively V, Nuseir N: Macrophage-induced angiogenesis is mediated by tumor necrosis factor-alpha. Nature 1987, 329: 630–632
53. Cybulsky MI, Chan MKW, Movat HZ: Biology of Disease. Acute inflammation and microthrombosis induced by endotoxin, interleukin-1, and tumor necrosis factor and their implication in gram-negative infection. Lab Invest 1988, 58: 365–378
54. Schmidt JA, Mizel SB, Cohen D, Green I: Interleukin 1, a potential regulator of fibroblast proliferation. J Immunol 1982, 128:2177–2182.
55. Sugarman BJ, Aggarwal BB, Hass PE, Figari IS, Palladino MA, Shepard HM: Recombinant human tumor necrosis factor-alpha: Effects on proliferation of normal and transformed cell in vitro. Science 1985, 230:943–945
56. Van Damme J, Opdenakker G, Simpson RJ, Rubira MR, Cayphas S, Vink A, Billiau A, van Snick J: Identification of the human 26-kD protein interferon beta2 (INF-beta2), as a B cell hybridoma-plasmacytoma growth factor induced by interleukin 1 and tumor necrosis factor. J Exp Med 1987, 165:914–919
57. Sironi M, Breviario F, Proserpio P, Biondi A, Vecchi A, van Damme J, Dejana E, Mantovani A: IL-1 stimulates IL-6 production in endothelial cells. J Immunol 1989, 142:549–553
58. Hirano T, Yasukawa K, Harada K, Taga T, Watanabe Y, Matsuda T, Kashiwamura S, Nakajima K, Koyama K, Iwamatsu A, Tsunasawa S, Sakiyama F, Matsui H, Takahara F, Taniguchi T, Kishimoto T: Complementary DNA for a novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin. Nature 1986, 324:73–76
59. Yabuhara A, Yanagisawa M, Murata T, Kawai H, Komiyama A, Akabane T, Masafumi I, Eiazaburou I, Junichiro F, Jun-Ichi H: Giant lymph node hyperplasia (Castleman's disease) with spontaneous production of high levels of B-cell differentiation factor activity. Cancer 1989, 63:260–265

Acknowledgments

The authors thank Dr. S. M. Goyert, Department of Rheumatology, Hospital for Joint Diseases, New York, NY; Dr. D. Y. Mason, Nuffield Department of Pathology, John Radcliffe Hospital, Oxford, U.K.; and Dr. C. J. L. M. Meijer, Department of Pathology, Free University of Amsterdam, Amsterdam, The Netherlands, for their gifts of monoclonal antibodies SG134, KP1, and HECA-452, respectively.

The excellent technical assistance of B. Smets, E. Van Dessel, C. van den Broeck, and the photographic work of M. Rooseleers are also appreciated.