

Inflammatory pseudotumour of the lung. Immunohistochemical analysis on four new cases

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Summary. Inflammatory pseudotumour of the lung (I.P.) is a quite rare benign lesion, variously named by different authors. In the present report four new cases of I.P. are presented and immunohistochemically studied with a panel of antibodies. Microscopically, the most prominent histological features were the presence of interlacing bundles of elongated histiocytic-like cells, plasma cell aggregates and lymphoid follicles. Immunohistochemistry showed that plasma cells are polyclonal. The spindle cells were negative for desmin, cytokeratins, lysozyme and S-100 and immunoreactive for alpha-1-antichymotrypsin, vimentin and for smooth-muscle alpha-actin. Actin and desmin, were clearly evident in the vessels' smooth muscle layers, highlighting the angioinvasive behaviour of the lesions. Our data are in keeping with literature suggesting that I.P. is due to a mixed histiocytic-myofibroblastic-reactive proliferation and support the inflammatory nature of IP.

Key words: Lung, Pseudotumour, Plasma-cell-granuloma, Immunohistochemistry

Introduction

Inflammatory pseudotumour of the lung (IP) is a quite rare benign lesion with a variable spectrum of histological aspects. IP has been variously named by different authors as xanthoma (Scott et al., 1948), xanthogranuloma (Alegre and Deust, 1958), histiocytoma (Makela et al., 1972), xanthomatous and inflammatory pseudotumour (Titus et al., 1962), xanthomatous pseudotumour (Buell et al., 1976), postinflammatory tumour (Kuzela, 1975), mast cell granuloma (Sherwin et al., 1965), plasma cell tumour (Cotton and Penido, 1952), plasma cell granuloma (Bahadori and Liebow, 1973), and plasma cell/histiocytoma complex (Spencer, 1984).

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Recently, Spencer (1984) pointed to the strict relationships between IP and lung histiocytomas, stating that the features of IP «blend imperceptibly with those of a histiocytoma and what has often been regarded and described as two different conditions are in fact two different stages in one continuing process». The process is probably an inflammatory/reactive one, mostly of cryptogenetic origin (Matsubara et al., 1988), where the spindle cells may be responsible for the evolution of the lesion from the most florid cases to the older, scarred and hyalinized lesions.

The aim of the present report is to investigate a group of four new cases of IP with a panel of antibodies/antisera, including histiocytic and smooth muscle markers, to assess further the nature of the spindle cell component and its evolution.

Materials and methods

We reviewed our surgical pathology files covering a three-year interval (1986-1989) and found four inflammatory pseudotumours of the lung. All specimens, obtained at surgery, were formalin fixed and paraffin embedded. Sections were stained with haematoxylin and eosin, Giemsa, Wilder silver impregnation for reticulin, PAS, PAS-diacetate, Congo red and Ziehl Neelsen. Immunohistochemical stains were performed on paraffin sections using the indirect immunoperoxidase method (Sternberger, 1979) or the avidin-biotin-complex technique (Hsu et al., 1981). The primary antisera/antibodies and positive controls are listed in table 1. Negative controls were obtained by omitting the primary antisera/antibodies, and substituting them with a corresponding non-immune serum or immunoglobulin.

Case histories:

Case n. 1

A 50-year-old man, smoker, suffering from mild

fever, underwent chest X-ray which disclosed a coin lesion in the left upper lobe. A wedge resection of the left upper lobe was made. The lung specimen contained a rounded yellowish-grey nodule, measuring 25x20x18 mm, not encapsulated but well circumscribed. The cut surface was fasciculated without necrosis or haemorrhage. The patient is alive and well after 2 years follow up.

Case n. 2

A 28-year-old man, smoker, with history of exposure to toxic paint, underwent routine chest X-ray, which revealed a coin lesion, 4 cm in diameter, in the middle left lung field. Bronchoscopy with aspiration cytology was negative. Transcutaneous fine needle cytology was not conclusive. A lobectomy of the superior lobe with lymphadenectomy was performed. The lobe contained a firm tumour, 3 cm in diameter, well circumscribed (Fig. 1), yellowish and fasciculated on cut surface. The patient is alive and well after 3 years follow up.

Case n. 3

A 53-year-old man, suffering from haemoptysis, underwent chest X-ray which disclosed a lesion in the left apical lobe. CT scan revealed a roundish solid lesion. Bronchoscopy with aspiration cytology was negative. Transcutaneous fine needle cytology was also negative. At surgery a wedge resection of the left superior lobe was made. Grossly the lung specimen contained a firm roundish nodule, 18 mm in diameter. The patient is alive and well after 2 years.

Case n.4

A 24-year-old woman was affected by moderate dyspnoea and non-productive cough for over one year, followed by slight fever and retrosternal pain. X-ray showed a wide opacity in the right lower lung field. Bronchoscopy showed an intraluminal round reddish mass obstructing the right bronchus. Brush cytology was characterized by large cells with one or more nuclei with prominent nucleoli, plasma cells, and spindle cells. The lesion was subsequently removed endoscopically. She was subsequently lost to follow up.

Results

Microscopically all the lesions are rather well demarcated, but not encapsulated. The most prominent histological features are the presence of interlacing bundles of elongated histiocytic-like cells, plasma cell aggregates and lymphoid follicles (Fig. 2). The spindle cells have abundant, finely granular cytoplasm, vesicular nuclei with finely dispersed chromatin and centrally placed nucleoli (Fig. 3). The plasma cells are mature and are interposed among the spindle cell bundles, sometimes with an «indian file» pattern (Fig. 4). Mast cells are abundant and ubiquitous. Foamy cells are also abundant, sometimes grouped in small nests

between the fusiform cells and contain granular PAS-positive material. Rare multinucleated cells are scattered throughout the lesion. Necrosis and mitotic figures are absent. A few bronchiolar structures as well as nests or alveolar macrophages are trapped within the tumours.

At the periphery of the lesions, the blood vessels show typical luminal involvement: the lumina are partly or totally occluded by a population of plasma cells and histiocytic-like fusiform cells (Fig. 5). Congo red stain for amyloid and Ziehl Neelsen stain for mycobacteria are negative.

Immunostaining for kappa and lambda light chains of the immunoglobulins reveals a polyclonal plasma cell population. The spindle cells are negative for desmin, cytokeratin, lysozyme and S-100 protein, and are immunoreactive for alpha-1-antichymotrypsin (Fig. 6), vimentin and for smooth-muscle alpha-actin. Actin-reactive spindle cells seem more abundant in the less hyalinized lesions and at the periphery of the tumours. The more centrally placed scarred areas are devoid of actin-reactive cells (Fig. 7A,B). Actin, as well as desmin, is clearly evident in the vessels' smooth muscle layers, highlighting the angioinvasive behaviour of the lesions. In fact, remnants of the muscular layer of medium sized arteries, completely invaded by the process, can be evidenced both at the periphery and in the inner areas of the lesions (Fig. 7C). Cytokeratins are clearly demonstrable in bronchiolar epithelia both in normal lung parenchyma and inside the lesions (entrapped bronchioli). Lysozyme is absent from the spindle cells, but clearly evident in some granulocytes and macrophages. A few S-100 protein-positive cells with dendritic morphology are scattered through the lesions.

Discussion

Approximately 300 cases of lung IP have been reported in the literature (Warter et al., 1987). Although they can occur at any age, they are most frequent in children and young adults. They are frequently symptomless and may be accidentally discovered during routine chest X-ray. Only one case is reported with clinical symptoms, which were related to hypercalcaemia due to calcitriol production by the pseudotumour (Helikson et al., 1986). Most cases are cryptogenetic, but in very few instances an infectious agent has been indicated as a putative aetiologic factor, I.E: *Coxiella burnetii* (Jaingan and Marrie, 1983) and mycobacteria (Loo et al., 1989). On histological grounds, IP should be distinguished from a variety of other neoplastic and non neoplastic lesions, particularly sclerosing haemangioma, pseudolymphoma and lymphomatoid granulomatosis (Fassina et al., 1986; Warter et al., 1987). Sclerosing haemangioma (Liebow and Hubbel, 1956) may resemble IP but is generally encapsulated and shows numerous lacunar spaces lined by flat or cuboidal cells, sometimes with papillary projections. Sclerosing haemangiomas are low grade neoplasms originating from respiratory epithelium and are positive for clara cell antigen and surfactant apoprotein

Table 1. Primary antisera and antibodies and positive controls used in the present study.

ANTISERUM/ANTIBODY	SOURCE AND CODE
Rabbit anti-lambda chain	Dako A193
Rabbit anti-kappa chain	Dako A191
Rabbit anti-lysozyme	Dako A099
Rabbit anti-A1ACT*	Dako A022
Rabbit anti-S-100	Dako Z311
Mouse anti-vimentin	Dako M725
Mouse anti-desmin	Dako M724
Mouse anti-cytokeratin	Lipshaw AE1/AE3
Mouse anti-actin	Sclavo 87174

*A1ACT: alpha-1-antichymotrypsin

The specimens contain a number of internal positive controls, i.e.: nerve fibre for S-100; endothelial cells for vimentin; muscular layers of arterioles for desmin and actin; mucosal epithelial cells of bronchioli for cytocheratin.

Positive controls for lambda and kappa light chains, lysozyme and A1ACT are sections of human lymph node.



Fig. 1. Case n. 2: Surgical specimen with circumscribed, roundish nodule.

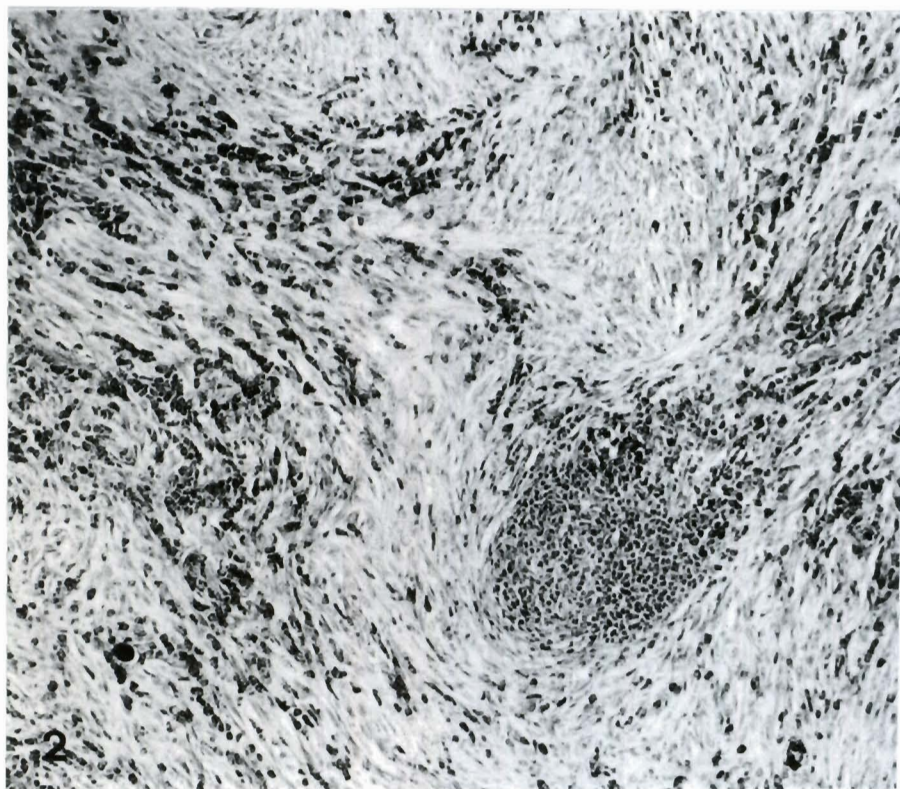


Fig. 2. The histological picture is characterized by interlacing bundles of elongated cells, plasma cells and lymphoid follicles. Giemsa stain. $\times 100$

(Nagata et al., 1985; Spencer and Nambu, 1986; Yousen et al., 1988). Pseudolymphoma (Carter and Eggleston, 1980) may be distinguished from IP on the basis of the characteristics of the lymphoid component: mature lymphoid cells are always abundant, with numerous plasma cells and lymphocytes, and, most important, there are many germinal centers.

It is very important to distinguish IP from lymphomatoid granulomatosis (Katzenstein et al., 1979), especially if IP shows prominent features of

«angioinvasiveness» (Warter et al., 1987). Lymphomatoid granulomatosis (LYG) generally shows bilateral lung involvement and, histologically, is characterized by a heterogeneous mononuclear cell population, with pleomorphic cells, sometimes reminiscent of Reed-Sternberg cells (Katzenstein et al., 1979; Barbareschi et al., 1985). This contrasts with the typical single coin lesion of IP and with its perfectly mature plasma cell infiltrate (Warter et al., 1987). Moreover LYG shows a predominant monoclonal

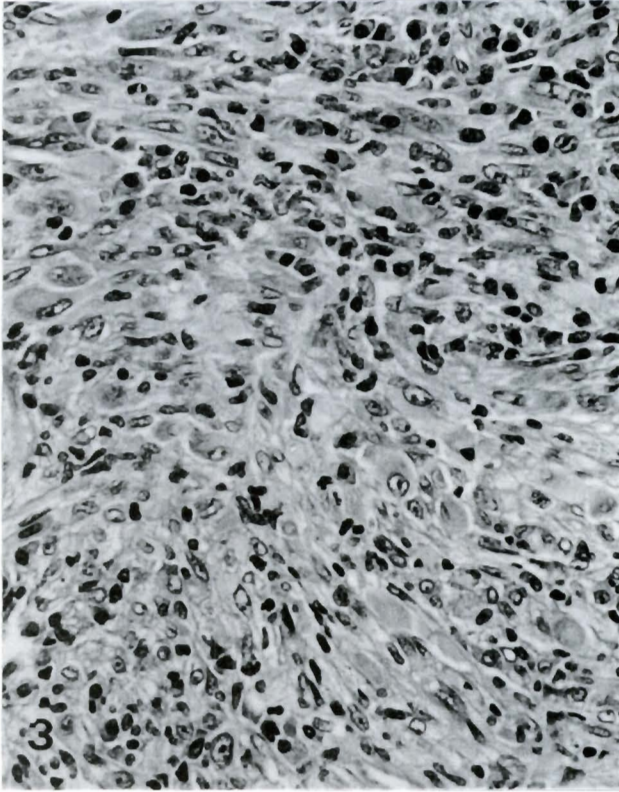


Fig. 3. Among the spindle and lymphoid cells there are some with epithelioid aspect, abundant granular cytoplasm, vesicular nuclei and small nucleoli. H-E. $\times 400$

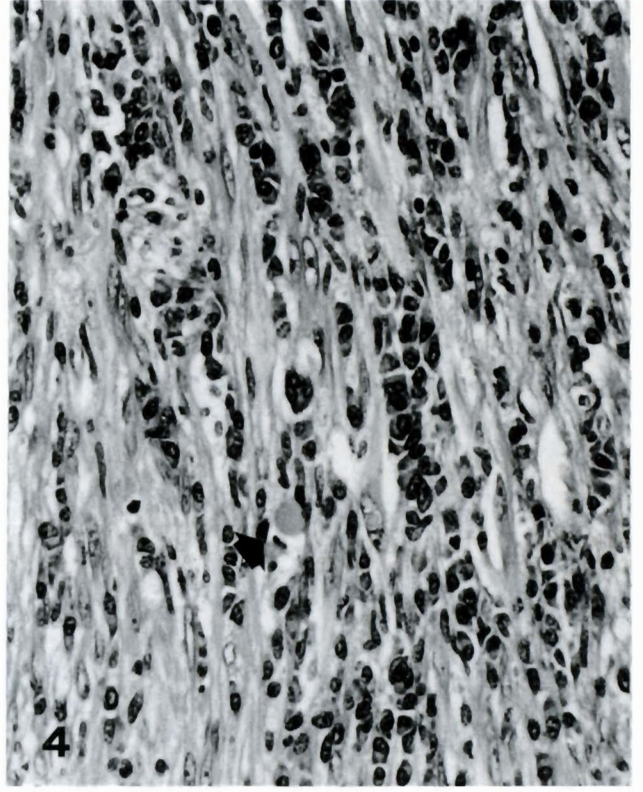


Fig. 4. Mature plasma cells interposed among the spindle cells showing «Indian file» pattern. A Russell body is clearly evident (arrow). Giemsa stain, $\times 400$

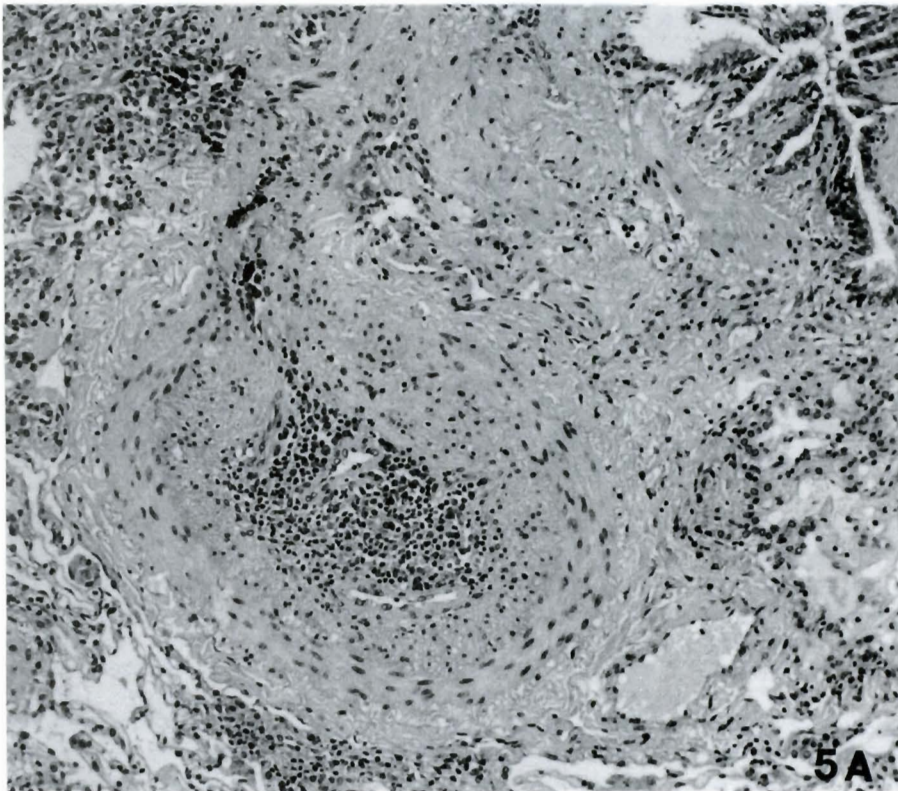


Fig. 5. A and B: The vessels at the periphery of the lesion are frequently occluded by plasma cells and histiocytic-like spindle cells. 5A: H-E $\times 100$; 5B: H-E $\times 400$

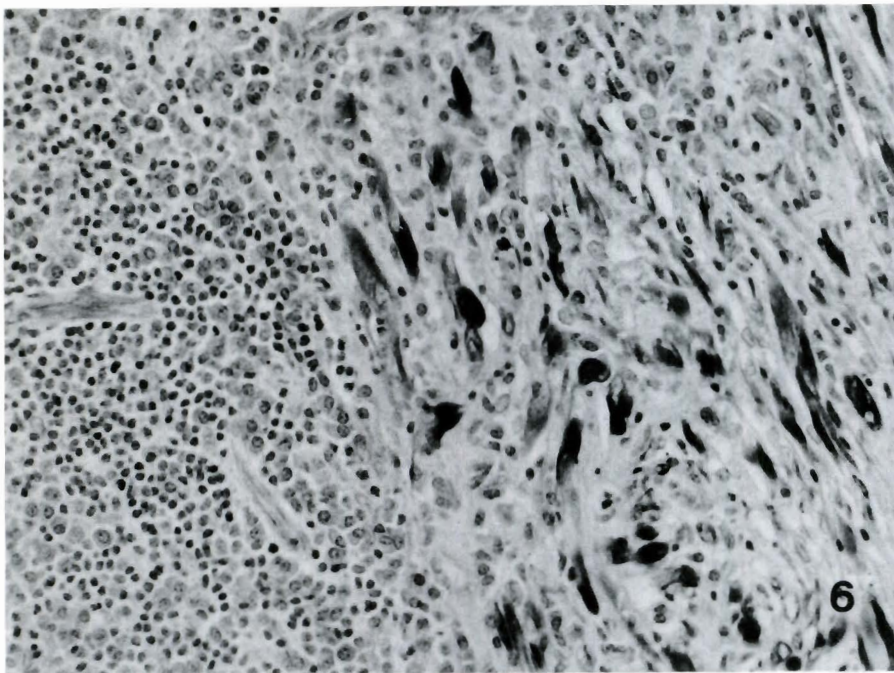
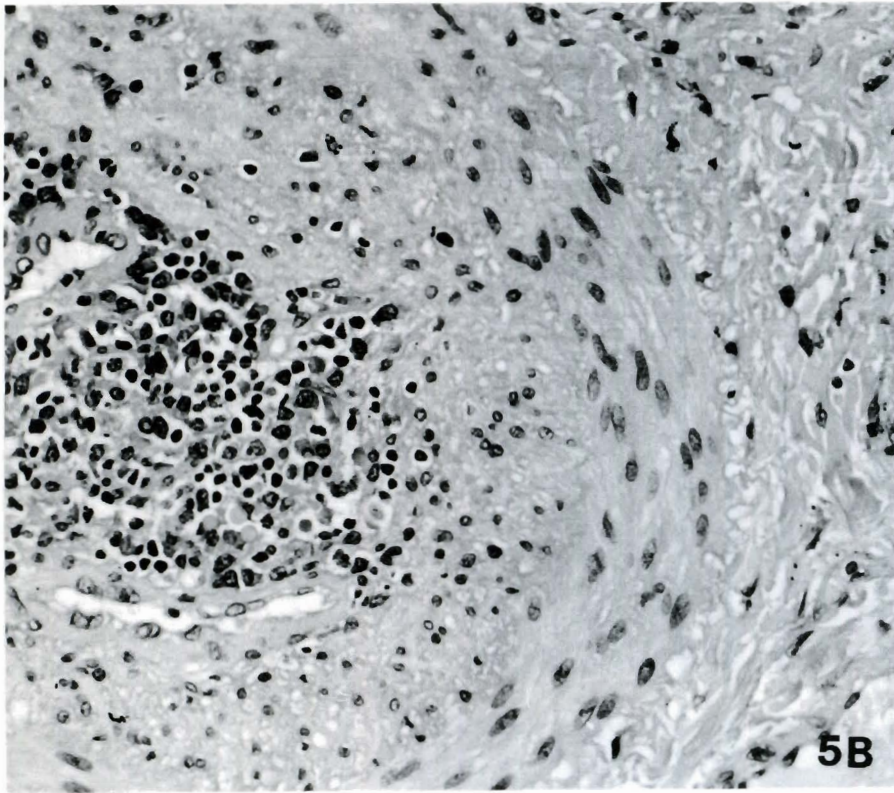


Fig. 6. Spindle cells are clearly immunoreactive for alpha-1-antichymotrypsin. Immunoperoxidase with nuclear counterstain (PAP), $\times 250$

plasma cell component, whereas IP has a polyclonal one (Warter et al., 1987).

Among other lung lesions, IP has to be distinguished from extramedullary plasmocytoma, with its generally monoclonal plasma cell component, nodular amyloidosis and pulmonary hyalinizing granuloma (Fassina et al., 1986).

The rare malignant fibrous histiocytoma of the lung is distinguishable on the basis of its more malignant cytohistological patterns (McDonnell et al., 1988).

Our present cases fulfill the histological diagnostic criteria of IP. Immunohistochemical analysis of our cases reveals a few interesting features. Firstly, as described by other authors (Fassina et al., 1986; Warter et al., 1987), the plasma cell component is polyclonal. Secondly, alpha-1-antichymotrypsin (A1ACT)-immunoreactivity is clearly present in most fusiform cells. Although A1ACT is not a strictly specific marker for histiocytes (Soini and Miettinen, 1988) its immunoreactivity in the spindle cells may favour a histogenetic relationship of these cells with histiocytes as similarly suggested by Rasmussen et al. (1989). In fact, similar immunohistochemical data are reported for malignant fibrous histiocytomas of the lung (Mc Donnell et al., 1988). A further immunohistochemical feature of our cases of IP is the staining of most fusiform cells for vimentin and of a part of them for actin, with concurrent absence of desmin immunoreactivity. Actin immunoreactivity, along with vimentin positivity and desmin negativity, support the hypothesis that at least a part of fusiform cells are myofibroblasts (Chen et al., 1983; Schuerch et al., 1984; Iwasaki et al., 1987; Tsukuda et al., 1987; Pettinato et al., 1989). Moreover, actin and desmin immunoreactivity highlights the invasion of the walls of the vessels by the tumour and seems to be a diagnostic tool for defining the angioinvasiveness of the lesion. Our immunohistochemical data are in keeping with previous ultrastructural studies on IP describing plasma

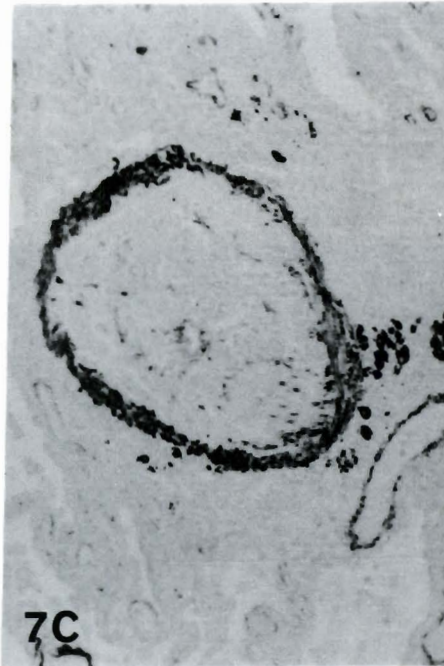
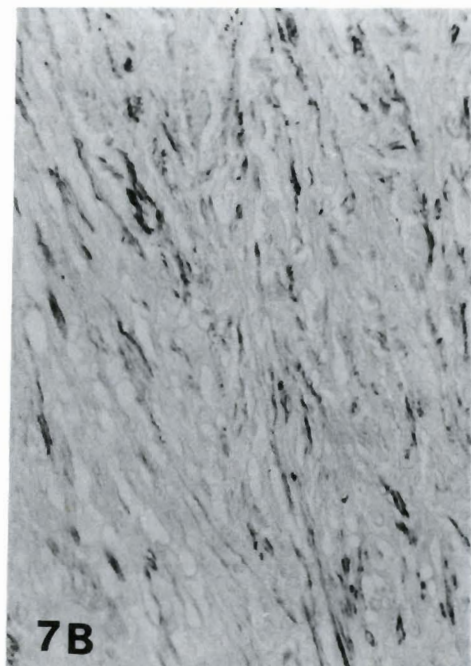
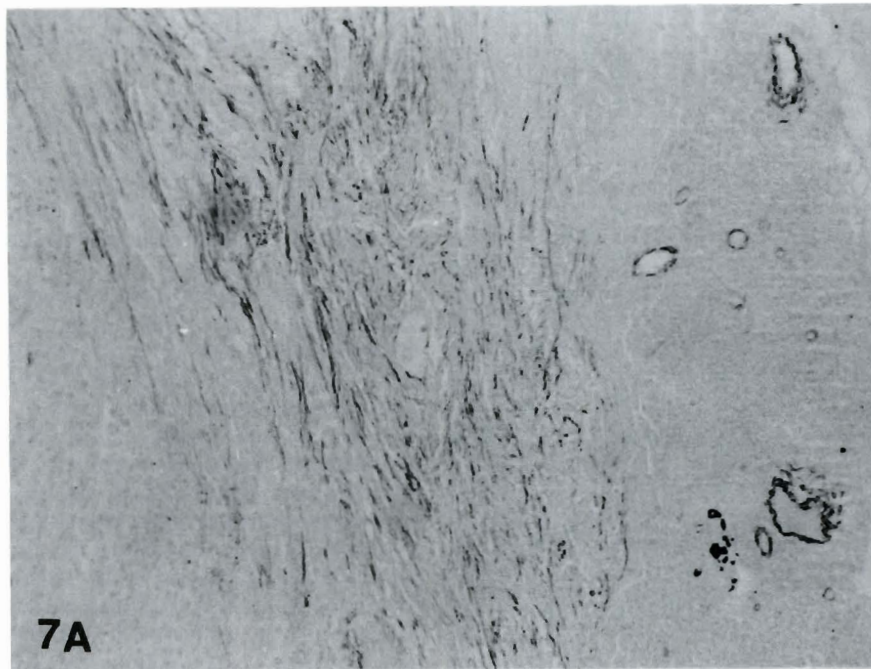


Fig. 7. A: Actin immunostaining clearly depicts the fusiform cells and the muscular layer of the vessels. The lymphoplasmacytic areas (left and right) are devoid of actin positive cells. **B:** Actin immunoreactivity is very delicate and do not every spindle cell is positive. **C:** Occluded vessel with prominent actin-positive muscular layer. Immunoperoxidase (PAP), A: $\times 100$, B: $\times 250$, C: $\times 100$

cells, mast cells, lymphocytes, macrophages, fibroblasts (Wentworth et al., 1968), undifferentiated mesenchymal cells (Kuzela et al., 1975) myofibroblasts, perivascular pericytic elements (Buell et al., 1976) and histiocytes (Sayjad et al., 1981; Alvarez-Fernández and Escalona-Zapata, 1983). Our data, suggesting a mixed myofibroblastic and histiocytic nature of the fusiform cell population and confirming the polyclonality of the plasma cell infiltrate, give further support to the inflammatory nature of IP (Matsubara et al., 1988).

Moreover, the presence of myofibroblasts may explain the evolution of the lesion from the stage of granuloma to the more collagenized, hyalinized and scarred older stages (Spencer, 1984). In this view, IP behave like the fibrohistiocytic pseudotumours at other sites (Lipper et al., 1980; Perrone et al., 1988), including nodular fasciitis (Enzinger and Weiss, 1988), the myofibroblast being responsible for both contraction of the lesion and hyalinization (Seemayer et al., 1983). In fact, in our cases actin immunoreactivity was somewhat stronger at the

periphery of the lesions, whereas the central scarred areas appeared devoid of actin-reactive fusiform cells.

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