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Inflammatory pseudotumour of the liver

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SUMMARY Five cases of inflammatory pseudotumour of the liver are reported and compared with seven individual previously published case reports. Clinical presentation was variable but often comprised low grade intermittent fever, vague abdominal symptoms, and a history of weight loss. Leucocytosis, raised erythrocyte sedimentation rate, and polyclonal hyperglobulinaemia were also sometimes detected. All five cases in the present series were considered to be clinically malignant; and in two the histological diagnosis was also that of malignancy.

The lesion is clearly inflammatory and reactive, but the aetiology remains unknown.

Most clinically detectable masses in the liver are malignant, and benign lesions, whether neoplastic or not, are rare. Recently, seven individual case reports have been published, describing a tumour like condition, occurring mostly in children or young adults, for which the term "inflammatory pseudotumour" seems to be appropriate.[1–7]

The mass in the liver is solitary but may be multiple, and microscopic appearances vary from case to case: a plasma cell component is invariably present and may predominate. Immunohistology has not been applied before to see whether this component is monoclonal or polyclonal nor to find out the nature of other cell types. A whorled pattern of fibrosis is often characteristic; neural or vascular elements have not been shown. Although variable, the clinical manifestations have been sufficiently severe to warrant a laparotomy and lead to surgical diagnosis of malignancy.

This paper reviews five further cases encountered over a period of five years from five different hospitals, including our own. All twelve cases are thought to represent a single entity originally described in the lung[8] and subsequently at other sites[9–16] under various names but with an identical pathology.

Case reports

CASE 1

A 10 year old girl had a one year history of recurrent attacks characterised by headaches, flushing, abdominal pain, diarrhoea, and vomiting. Extensive investigations at three hospitals could find no cause. Her white cell count was occasionally raised with up to 75% neutrophil polymorphs, her erythrocyte sedimentation rate was persistently around 50–70 mm/hour, and all classes of immunoglobulins were raised. An exploratory laparotomy was carried out but no abnormality was found. The appendix, a mesenteric lymph node, and a sample of muscle were removed. These were histologically normal. Her attacks continued over the next six months. An abdominal aortogram was carried out to look for evidence of polyarteritis nodosa. This showed an abnormality of hepatic vasculature, which, on further investigation by ultrasonography and radioisotope scan, proved to be a solid mass in the right lobe of the liver. A month later a right hepatic lobectomy was carried out, and a hard, solitary, tumour like lesion 9 cm in diameter was removed. The histological appearances were unusual, and various diagnoses were suggested, including hamartoma, Hodgkin's disease, and a tumour of neurogenic origin. She was completely symptom free eight years after surgery.

CASE 2

A 61 year old man was admitted with fever of unknown origin after a holiday in Corfu. The only abnormalities on investigation were a white cell count of 13×10^9 with 73% neutrophil polymorphs, an erythrocyte sedimentation rate of 56 mm/hour, and mildly deranged liver function tests. Rounded opacities were seen on chest x-ray in both lower lobes, and ultrasonography showed multiple large lesions in the liver. At laparotomy multiple liver nodules were found up to 3 cm in size; one of these was biopsied. The histological appearances were thought to be

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those of an anaplastic malignant tumour. The patient was considered to be unsuitable for multiple chemotherapy and he was given prednisone alone. He was discharged home from terminal care but he returned a year later with a squamous cell carcinoma of his right ear. All his symptoms had disappeared in the interim, and his chest x-ray, liver function tests, and ultrasound scan showed normal results. He remained alive and well five years later.

CASE 3

An Indian child born in the Punjab came to live in London with his parents at the age of 3 years. He last visited India six years before the onset of symptoms and had remained well in the interim. He presented at the age of 12 with three months' history of lethargy, vague abdominal pain, and night sweats. On admission his liver was enlarged and tender. Extensive investigations produced negative results with the exception of 20% eosinophilia, raised IgG and IgM values, and an ultrasound scan that showed an area of abnormality in the liver close to the gall bladder bed. At laparotomy a hard mass 5 cm in diameter was found in the anterior edge of the liver with omentum adhering to it. The rest of the liver showed a scatter of small white nodules. The gall bladder was mobilised and the mass excised. The histological appearances were interpreted as those of a chronic inflammatory mass of uncertain aetiology, possibly parasitic, syphilitic, or tuberculous. Culture of the tissue yielded negative results. The patient made an uneventful recovery and remained well four years later. Stools were repeatedly tested for parasites but none was found, and his eosinophilia disappeared after surgery.

CASE 4

A 44 year old West Indian man had had a seven year history of painless intermittent jaundice. Endoscopic retrograde cholangiopancreatography showed stricture of the common bile duct just proximal to the sphincter of Oddi. This was treated by cholecystojejunostomy. Three years later he developed unremitting obstructive jaundice. Repeat endoscopy and contrast injection study showed stricture of the common hepatic duct, which was treated by the insertion of an endoprosthesis. Ultrasonography performed after the procedure showed a mass surrounding the stricture. At laparotomy multiple nodules up to 2 cm in diameter were found in the liver and two of these were biopsied. Histological examination did not establish the precise nature of the lesion, but possibilities included a tumour of histiocytic, vascular, or neural origin. The stricture was excised and a choledochojejunostomy was done. The patient remained well four months after surgery.

CASE 5

A 57 year old man was admitted as an emergency with a five day history of nausea, vomiting, and upper abdominal pain, which had been followed by fever and jaundice. Total white cell count was 23×10^9 with 93% neutrophil polymorphs. A plain x-ray of the abdomen showed multiple gall stones. The condition responded well to conservative management with antibiotics, and the patient was discharged home. He was readmitted six weeks later. At laparotomy a shrunken fibrous gall bladder was found that contained stones; a stone was also found impacted at the lower end of the common bile duct where it was surrounded by a fibrous mass. Cholecystectomy and a wedge resection of the ampulla of Vater were carried out with reanastomosis of the ducts. Multiple, white, fibrous nodules were present in the liver up to 2 cm in diameter and these were thought to be metastases from carcinoma of the common bile duct: one of these was biopsied. The histology was correctly interpreted

Table 1 *Inflammatory pseudotumour of liver: summary of seven previously reported cases 1953–84*

Reference	*Age (in years) and sex*	*Presentation*	*Solitary or multiple*	*Site*	*Size*	*Treatment*	*Outcome*
Pack and Baker 1953[1]	40 M	Fever, weight loss, right upper abdominal mass; white cell count $14{\cdot}8 \times 10^9$/l with 34% eosinophils	Solitary	Right lobe of liver	25 × 13 cm	Right hepatic lobectomy	Recovery
Haith *et al* 1964[2]	6 M	Fever, vomiting, jaundice, pruritus, weight loss	Solitary	Porta hepatis	3 cm	Pancreaticoduodenectomy	Malabsorption
Hertzer *et al* 1971[3]	1 F	Fever, jaundice, hepatomegaly; white cell count 13×10^9/l	Solitary	Porta hepatis	?	Biopsy	Portal hypertension
Someren 1978[4]	4½ M	Fever, malaise	Solitary	Right lobe of liver	15 × 12 cm	Right hepatic lobectomy	Recovery
Paineau *et al* 1983[5]	46 M	Fever, weight loss, hepatomegaly; white cell count 17×10^9, ESR 80/first hour, hyperglobulinaemia	Solitary	Right lobe of liver	7 cm	Right hepatic lobectomy	Recovery
Chen 1984[6]	29 M	Fever, weight loss, mass in liver	Solitary	Right lobe of liver	6 cm	Wedge resection	Recovery
Heneghan *et al* 1984[7]	8 F	Anorexia, abdominal pain, jaundice	Multiple	Right lobe of liver	?	Biopsy followed by total hepatectomy and transplantation	Recovery

One of two cases reported by Hertzer *et al*[3] had focal nodular hyperplasia.
ESR = erythrocyte sedimentation rate.

Table 2 *The principal histological features of five cases of inflammatory pseudotumour of liver*

Case No	*Solitary or multiple*	*Site*	*Size*	*Plasma cells*	*Oval or spindle cells*	*Fibrosis*	*Additional findings*
1	Solitary	Right lobe of liver	9 cm	+ + +	+ +	Uniform, laminated, and whorled	None
2	Multiple	Both lobes of liver	Up to 3 cm	+ + +	+	Focal, laminated	Endophlebitis, granulomas, immature lymphoid cells
3	Solitary	Right lobe of liver	5 cm	+ + +	+ +	Focal, whorled	Eosinophils, Russell bodies
4	Multiple	Both lobes of liver	Up to 2 cm	+ +	+ + +	Uniform, laminated, and whorled	Lymphoid follicles, entrapped neural elements
5	Multiple	Both lobes of liver	Up to 2 cm	+ +	+ + +	Uniform	Granulomas

as inflammatory and reactive. The patient made an uneventful recovery and remained well two months after surgery.

Table 1 summarises the salient clinical features of seven previously published case reports. The histological appearances were the same with some minor variations and had been described as inflammatory pseudotumour, plasma cell granuloma, or histiocytoma. Infection as a possible aetiology was suggested in only one case,[5] the rest being described as of unknown cause.

HISTOPATHOLOGY

Sections were stained with haematoxylin and eosin, Martius scarlet blue, Gordon and Sweet's reticulin, periodic acid Schiff with and without diastase, Gram, and the peroxidase-antiperoxidase immunoperoxidase method for heavy and light immunoglobulin chains, lysozyme, α-1-antitrypsin, S100 protein, and factor VIII related antigen. The microscopic appearances were essentially the same, though they varied in detail. Table 2 shows the main histological features and Table 3 the results of immunohistology. Semiquantitative scoring was expressed from absent (−) to present (+ to + + + +).

All masses, whether solitary or multiple, were well defined and expansile with a fibrous capsule of variable thickness (Fig. 1). The surrounding liver showed an inflammatory or fibrous reaction in portal tracts, both of which were usually mild. In cases 2 and 5 scanty suppurating granulomas were seen away from the mass (Fig. 2)

The inflammatory cell content consisted mainly of plasma cells in all cases (Fig. 3) and was the predominant feature in cases 1, 2, and 3. Extracellular Russell bodies were common in case 3. The plasma cells were polyclonal, secreting IgG (mainly), Iga (less commonly), and IgM (rarely) heavy chains and both κ and λ light chains in all cases (Figs. 4a and b). Lymphocytes varied from being scanty and mature to numerous and immature, particularly in case 2. Some of these also showed a polyclonal pattern of staining for immunoglobulin heavy and light chains. Lymphoid aggregates, some with germinal centres, were seen around the periphery in case 4. Neutrophil polymorph leucocytes were generally few, but eosinophils were numerous in case 3.

Oval to spindle cells were the next most commonly seen and predominanted in cases 4 and 5 (Fig. 5a). Some had large vesicular nuclei and prominent nucleoli, resembling mononuclear Hodgkin's cells. Many of these reacted positively for histiocyte markers lysozyme and α-1-antitrypsin (Fig. 5b). Multinucleate giant cells were few but when present were widely scattered (Fig. 5c).

A tendency to fibrosis with a whorled laminated pattern was striking and was particularly noticeable in cases 1, 4, and 5 where, in areas, the resemblance to a neurofibroma was close (Fig. 6). Large nerves were entrapped in the mass in case 4 in which the lesion was situated close to the porta hepatis. All masses were poorly vascularised and small slit like spaces, staining positively with factor VIII related antigen were few and randomly scattered. In case 2 endophlebitis of small to medium sized veins was seen (Fig. 7).

Organisms could not be shown in any of the five cases.

Table 3 *Results of immunohistology*

Case No	*IgA*	*IgM*	*IgG*	*IgE*	*κ*	*λ*	*Lysozyme*	*α-1-antitrypsin*	*S100 protein*	*Factor VIII related antigen*
1	+ +	+	+ + + +	−	+ + + +	+ + +	+ + + +	+ +	−	+
2	−	−	+	−	+	+	+ +	+	−	−
3	+	+	+ + +	+	+ +	+ + +	+ +	+	−	+
4	+	−	+ +	−	+	+	+ + +	+	−	−
5	+ +	+	+ +	−	+ +	+ +	+ +	+	−	+

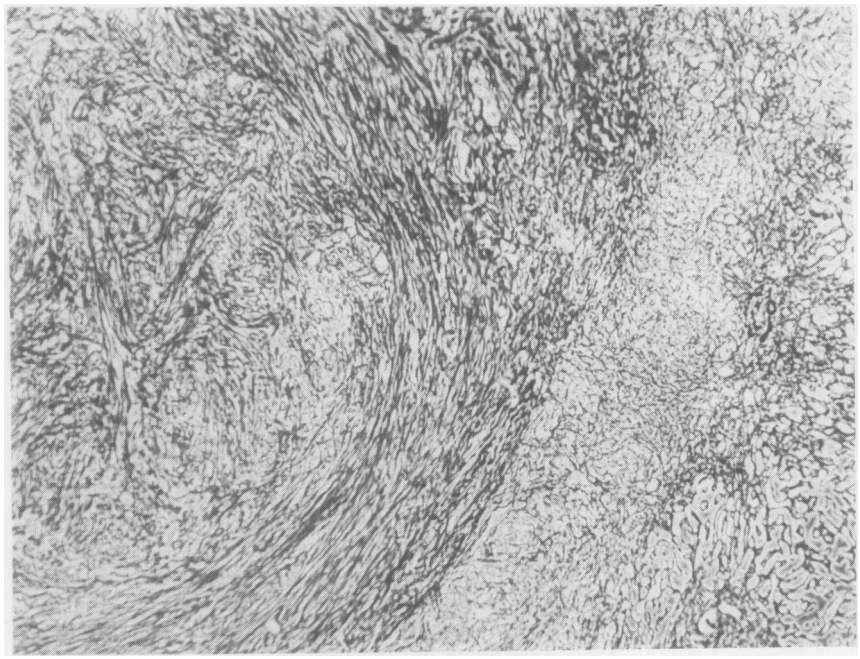

Fig. 1 *Well defined mass on the left is separated from surrounding liver on the right by thick fibrous capsule. (Gordon and Sweet's reticulin.)* × *80.*

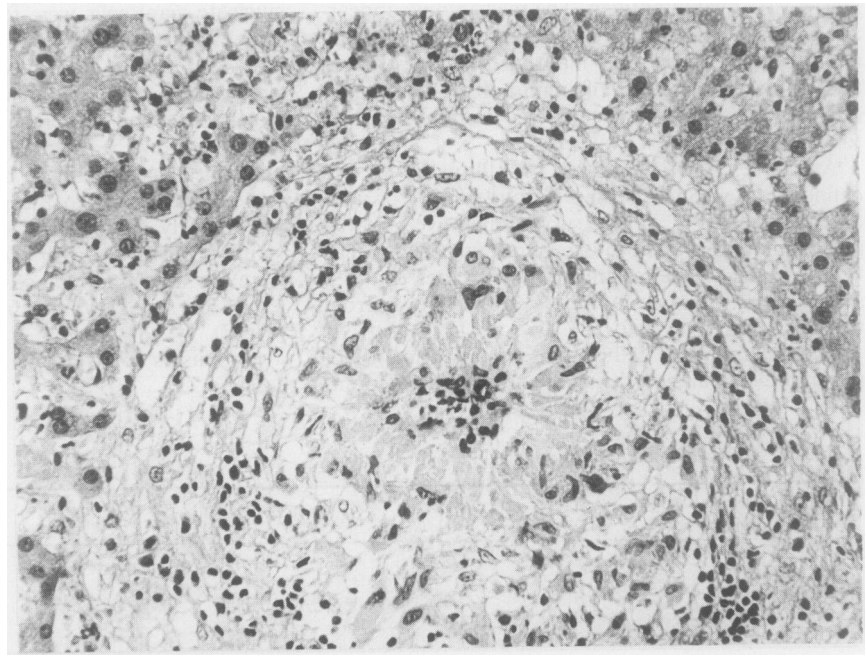

Fig. 2 *Granuloma in portal tract with necrotic centre containing neutrophil polymorph leucocytes. (Haematoxylin and eosin.)* × *300.*

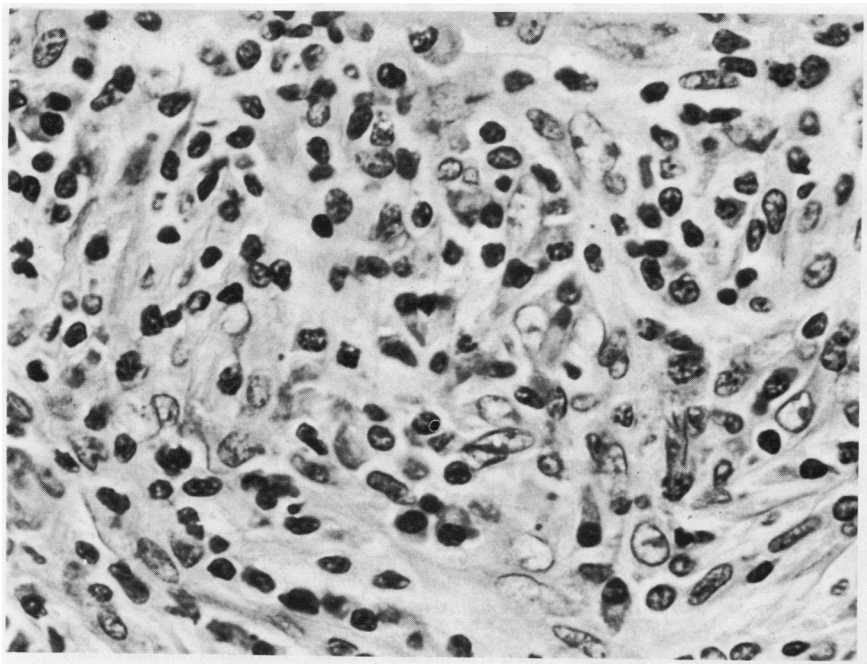

Fig. 3 *Numerous plasma cells mixed with lymphocytes and large mononuclear cells with vesicular nuclei. (Haematoxylin and eosin.)* ×800.

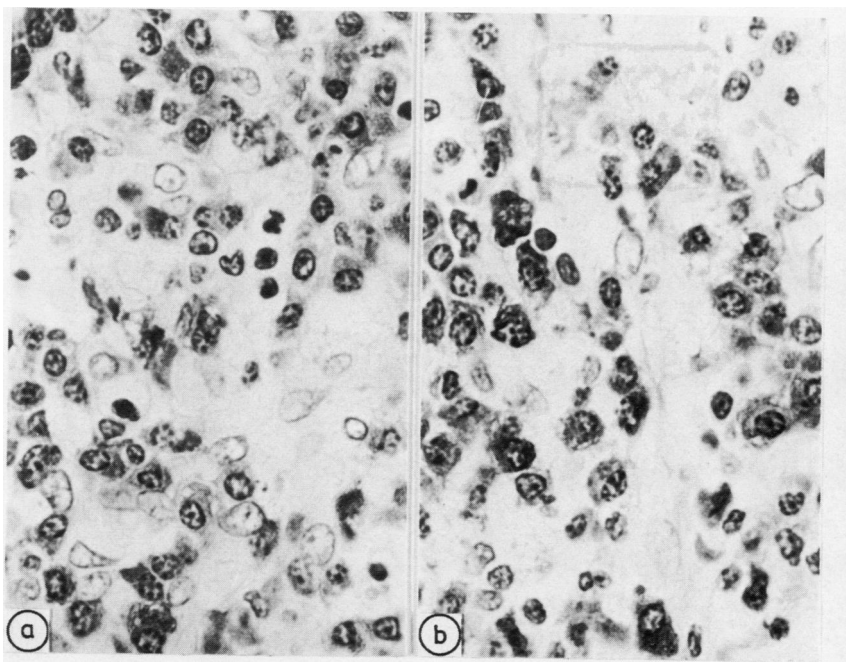

Fig. 4 *Plasma cells and some lymphocytes stain positively (dark) for kappa (a) and lambda (b) light chains. (Peroxidase-antiperoxidase.)* ×800.

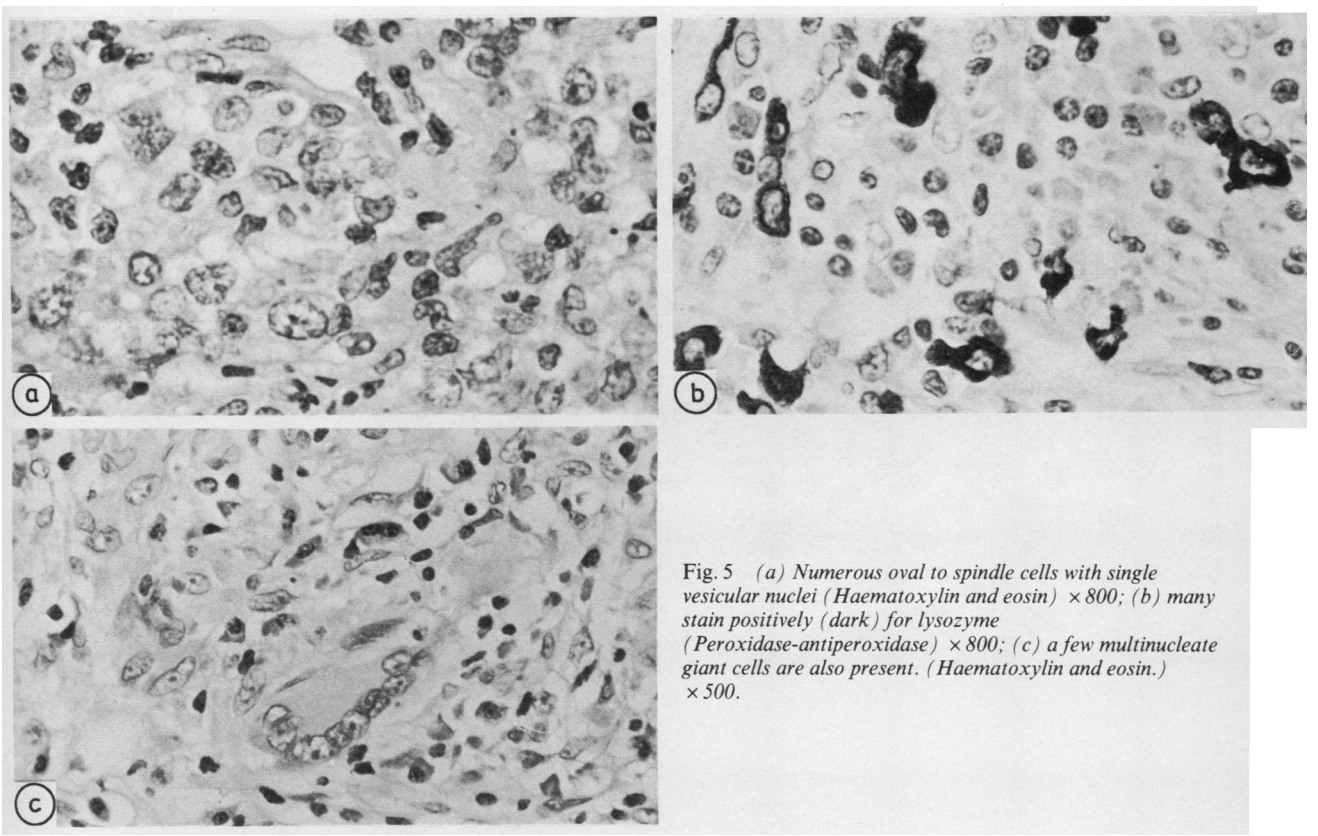

Fig. 5 *(a) Numerous oval to spindle cells with single vesicular nuclei (Haematoxylin and eosin) ×800; (b) many stain positively (dark) for lysozyme (Peroxidase-antiperoxidase) ×800; (c) a few multinucleate giant cells are also present. (Haematoxylin and eosin.) ×500.*

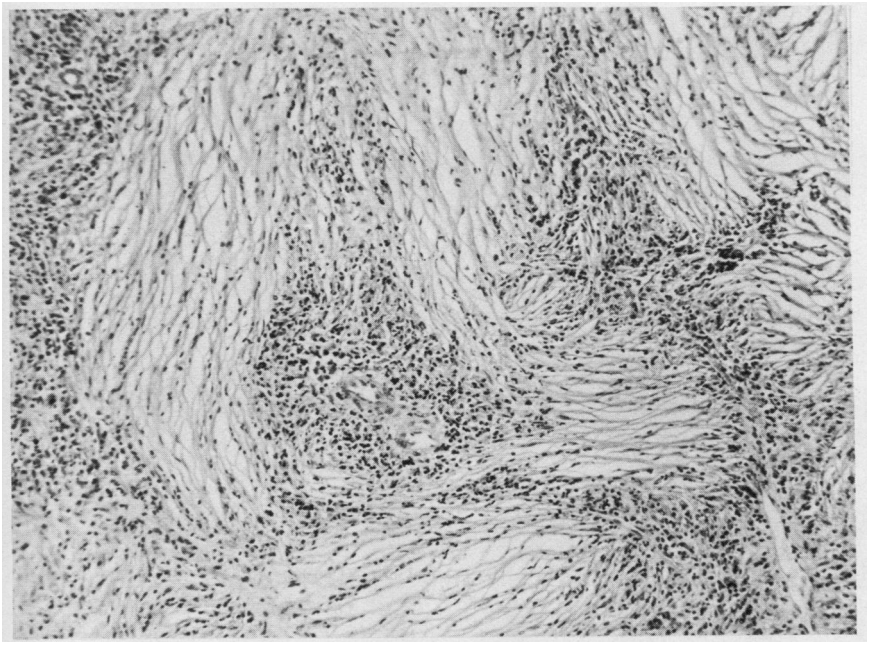

Fig. 6 *Characteristic whorled laminated pattern of fibrosis. (Gordon and Sweet's reticulin.) ×125.*

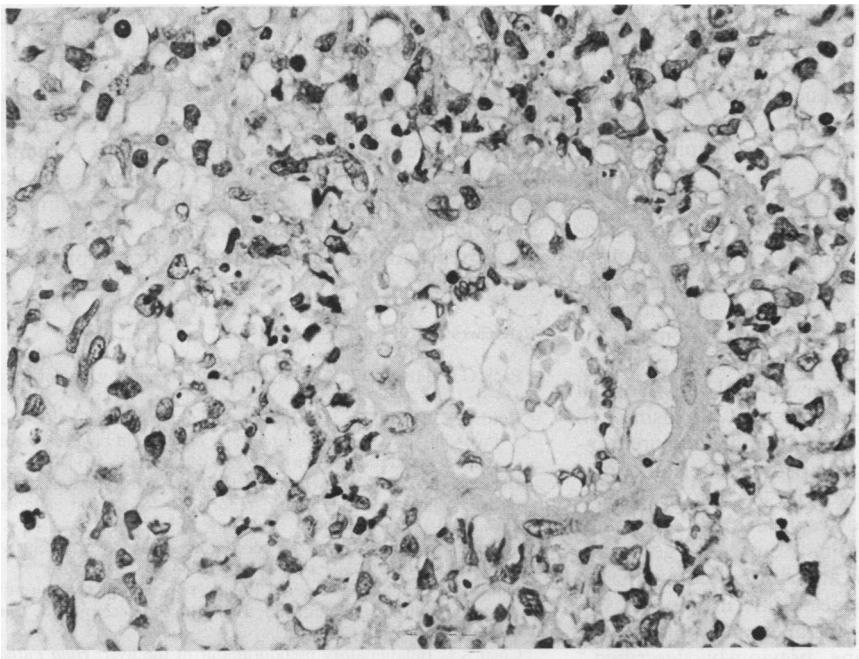

Fig. 7 *Endophlebitis within mass. (Haematoxylin and eosin.)* ×*500.*

Discussion

Inflammatory pseudotumours remain a clinicopathological enigma. In their classical account of 40 pulmonary cases Bahadori and Liebow[8] preferred to use the term "plasma cell granuloma," but many other synonyms have been used to describe the same lesion before and since. These include "histiocytoma," "pseudolymphoma", and even "plasmacytoma," which is regrettable as this term definitely denotes a neoplasm. The profusion of terms is undoubtedly due to the variability of histological appearances from case to case, but plasma cells are always present. The lung remains the most common primary site: the lesion is usually asymptomatic and detectable on routine chest x-ray examination, most commonly in children and young adults. Subsequently, tumour like lesions with the same histology have been described at other sites, notably stomach, retroperitoneum, ovary, kidney, spleen, spinal cord, meninges, and brain.[9-16] Some examples of the well known "pseudotumour of the orbit"[10] are probably of the same ilk. At all sites inflammatory pseudotumours clinically masquerade as malignant growths. This impression is strengthened by the lack or paucity of symptoms.[16] A history of trauma or surgical operation is rarely obtained, that of an acute infective episode never, and the many types of associated disorders described are probably all fortuitous.[16] In rare instances when tissue was cultured no organisms could be grown.[16]

When inflammatory pseudotumour occurs in the liver it seems to differ little in its clinical manifestations from similar lesions at other sites, and there were no important differences between the previously reported seven cases and the present series of five when all twelve were analysed together. Six patients were children 12 years of age or less, and another was a young adult of 29. The clinical manifestations were often vague. The commonest presenting symptoms were low grade intermittent fever over weeks or months in nine patients, abdominal pain often with vomiting or diarrhoea, or both, in six, and probably some weight loss in all, which was prominent in four. Five patients became jaundiced. In two patients (both adults) cholelithiasis was present. Intermittent leucocytosis was recorded in seven patients and eosinophilia in two; a search for intestinal parasites proved negative in both. A raised erythrocyte sedimentation rate or polyclonal hyperglobulinaemia, or both, were found in three patients. Extrahepatic lesions in the lung were seen on chest x-ray in one case. Clinically, liver enlargement with or without a mass was detected in all cases and was regarded as malignant. At operation the lesion was solitary in eight and multiple in four. Its size varied from 2 cm to 25 cm. The right lobe of the liver was affected in six cases, both lobes in three, and the porta hepatis in three. All but four patients recovered after surgery; one developed malabsorption, one portal hyper-

tension, and two have only been operated on recently and may continue to have further problems associated with reconstruction of the common bile duct. Two patients, who were considered to have inoperable malignancy, were given steroids and made a complete recovery as a result of, or in spite of, this treatment.

The initial histological diagnosis in the present series was some sort of a tumour in three and a malignancy in two; in the remaining two the inflammatory nature of the lesion was recognised at the outset. In the previously recorded seven cases[1-7] inflammatory pseudotumour, plasma cell granuloma, or histiocytoma were correctly diagnosed—evidently with some difficulty and after referral. Histological appearances cover a wide range, but a plasma cell component is invariably present and may predominate. Oval or spindle shaped cells, sometimes arranged in fascicles or whorls, are the next most commonly seen. Lymphocytes, which are sometimes immature, occasional germinal centres, large mononuclear cells, eosinophils, and fibrosis complete the picture. Granulomas were seen only in two cases in the present series and intrahepatic portal vein endophlebitis in two, one previously described.[4] Micro-organisms were thoroughly searched for by histological staining methods in all cases in the present series and in three previously published cases,[1 2 4] but none was found.

Immunohistology was carried out for the first time in the present series of five cases, and the non-neoplastic polyclonal nature of the plasma cell component was definitely established. The histiocyte markers lysozyme and α-1-antitrypsin were positive in some, though not all, large mononuclear or oval shaped cells. The rest, particularly spindle cells, were presumably fibroblasts; none reacted with anti-S100 protein antibody, though strongly staining neural elements were present, particularly in lesions near the porta hepatis. These must represent normal structures entrapped in the lesion. Factor VIII related antigen was present in the lining of scant slit like spaces, but, in general, a vascular component was minimal. It seems that the liver may be the second most common site for inflammatory pseudotumour after the lung, and this lesion must enter into the differential diagnosis of obscure, complex, but generally inflammatory lesions, the chief characteristic of which is polyclonal proliferation of plasma cells. Recovery is usual, unless the main hepatic or common bile ducts are affected. The aetiology, as at other sites, remains unknown.

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