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Synovial biopsy in haemochromatosis arthropathy

Histological findings and iron deposition in relation to total body iron overload

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The existence of a specific disorder of the joints in patients with idiopathic haemochromatosis was first suggested by Schumacher (1964) and in a recent survey of our patients we found evidence of an arthropathy in 31 of 54 male patients (Dymock, Hamilton, Laws, and Williams, 1970). The joints most frequently involved were the metacarpophalangeals but larger joints were also affected and such patients may be severely disabled. Chondrocalcinosis was present in 22 of the 54 male patients and, although it was occasionally found without signs of joint involvement, we did find a correlation between such hyaline cartilage calcification and joint damage.

Deposits of haemosiderin in the cartilage and synovium were recorded by Sheldon (1935) and these could be directly responsible for initiating joint damage.

In this paper we describe the histological appearances and the incidence of iron deposition in the synovium obtained mainly by needle biopsy in 27 patients. Some of them were untreated and others at varying stages during or after completion of venesection therapy. The findings are related to clinical and radiological evidence of arthropathy and to measurements of liver and total body iron stores.

Patients and methods

The diagnosis of haemochromatosis had been made according to clinical, biochemical, and histological criteria (Williams, 1968). Six of the 27 patients were untreated at the time of the initial study, three were having multiple venesection therapy, and eighteen had completed multiple venesection between 2 months and 7 years previously. One asymptomatic relative was included who had significant hepatic siderosis and fibrosis and who was found on radiological examination to have articular chondrocalcinosis.

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In 22 patients, synovial tissue was obtained from the knee joint by needle biopsy and in the remainder at autopsy. Cartilage was also examined in the five autopsy specimens. The tissue was fixed in formal saline, and sections (5 μ.) were cut and stained with haematoxylin and eosin and by Perl's technique for iron. They were examined under polarized light for the presence of the birefringent crystals of calcium pyrophosphate. In two patients half the biopsy was fixed in absolute ethanol as recommended by Schumacher (1968) for the preservation of calcium pyrophosphate crystals. This practice was discontinued when parallel experience with biopsies from patients with idiopathic chondrocalcinosis demonstrated adequate preservation in formalin-fixed material (Atkins, McIvor, Smith, Hamilton, and Williams, 1970). In each case the sections were examined without knowledge of the clinical status of the patient.

The serum iron and iron-binding capacity were measured and in all patients the total chelatable body iron stores were measured using the differential ferrioxamine test (Fielding, 1965; Smith, Lestas, Miller, Dymock, Pitcher, and Williams, 1969). Seventeen patients had had a recent liver biopsy performed and the amount of iron was graded from 1 to 4 (Scheuer, Williams, and Muir, 1962).

Results

In assessing the histological appearances the minor changes have been ignored, and those shown in Table I (opposite) were considered to represent significant abnormalities. Haemosiderin deposits were demonstrated on histological examination in eleven patients and when present were always within synovial intimal cells. Deposits were also seen within the phagocytic cells of the superficial stroma in eight cases (Fig. 1, opposite). No iron could be demonstrated in the five specimens of cartilage obtained at autopsy, although in three of these patients iron was seen in the synovium.

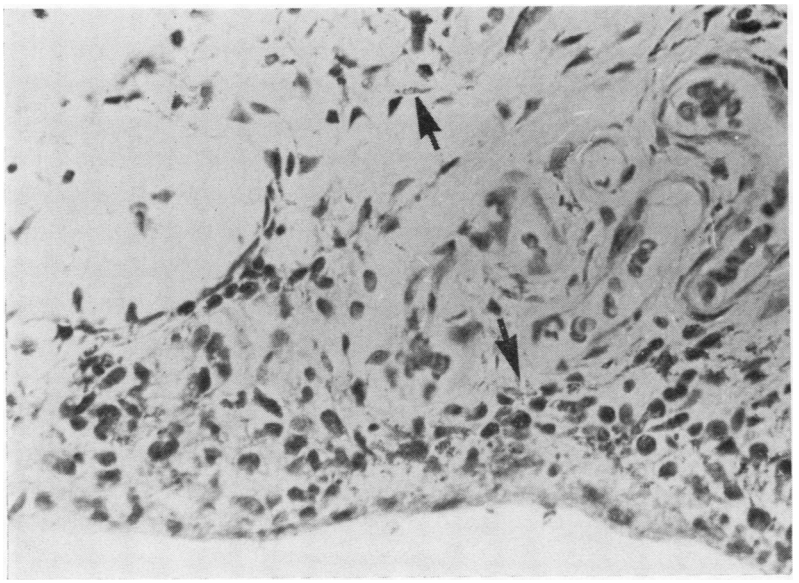

FIG. 1 *Synovium containing much haemosiderin (arrowed) lying in the cells of the stroma and in the intimal cells. Haematoxylin and eosin.* × 420.

Table I *Relationship of histological abnormalities to the presence or absence of iron in the synovium and to radiological evidence of arthropathy*

Histological Abnormalities	*No. of cases*	*Synovial iron present*	*Radiological arthropathy present*
Intimal cell hyperplasia	Present 8	5	5
	Absent 19	6	14
Villus formation	Present 7	5	5
	Absent 20	6	14
Chronic inflammatory cell infiltrate	Present 2	1	1
	Absent 25	1	1
Total cases	27	11	19

Intimal cell hyperplasia was present in eight patients and was often striking. In Fig. 2*a* this is shown at the tip of a villus and in that case a chronic inflammatory cell infiltrate in the stroma was also present (Fig. 2*a*, *b*, overleaf).

The latter feature was present in one other patient. Villus formation was present in seven cases. No relationship could be found between these histological abnormalities and the radiological evidence of an arthropathy.

No crystals of calcium pyrophosphate were seen in the synovium but white crystalline material was found in the menisci and cartilage from three of the autopsy cases, and in the two cases examined by *x* ray diffraction crystallography this was shown to be calcium pyrophosphate dihydrate (Dr. J. D. Sutor, University College, London).

Relationship of synovial iron deposition to arthropathy, stage of venesection therapy, and body iron stores

Each patient had a complete skeletal survey. Nineteen had radiological features of an arthropathy at the time of the study, of whom seventeen had symptoms. Iron was present in the synovium of eight of these patients as compared with three of the eight without radiological abnormality.

There was a definite relationship between the presence of synovial iron and the stage of treatment (Table II). In four of the eighteen patients who had completed venesection therapy, synovial iron was present, whereas it was found in seven of the nine patients who were untreated or who had just started multiple venesection therapy.

Table II *Relationship of synovial iron to venesection therapy and to radiological evidence of arthropathy*

Synovial iron	*No. of cases*	*Stage of venesection therapy*			*Radiological arthropathy present*
		Before	*During*	*After*	
Present	11	4	3	4	8
Absent	16	2	1	13	11
Total	27	6	4	17	19

Since this suggested that iron could be mobilized in the same way as iron deposits in other sites, the synovial iron was then related to the total body iron stores as assessed by the differential ferrioxamine test (Fig. 3). Although there is some overlap between the two groups, the mean chelatable iron stores in those with synovial iron was considerably higher at 1,198 μg./kg. than the corresponding value of 470 μg./kg.

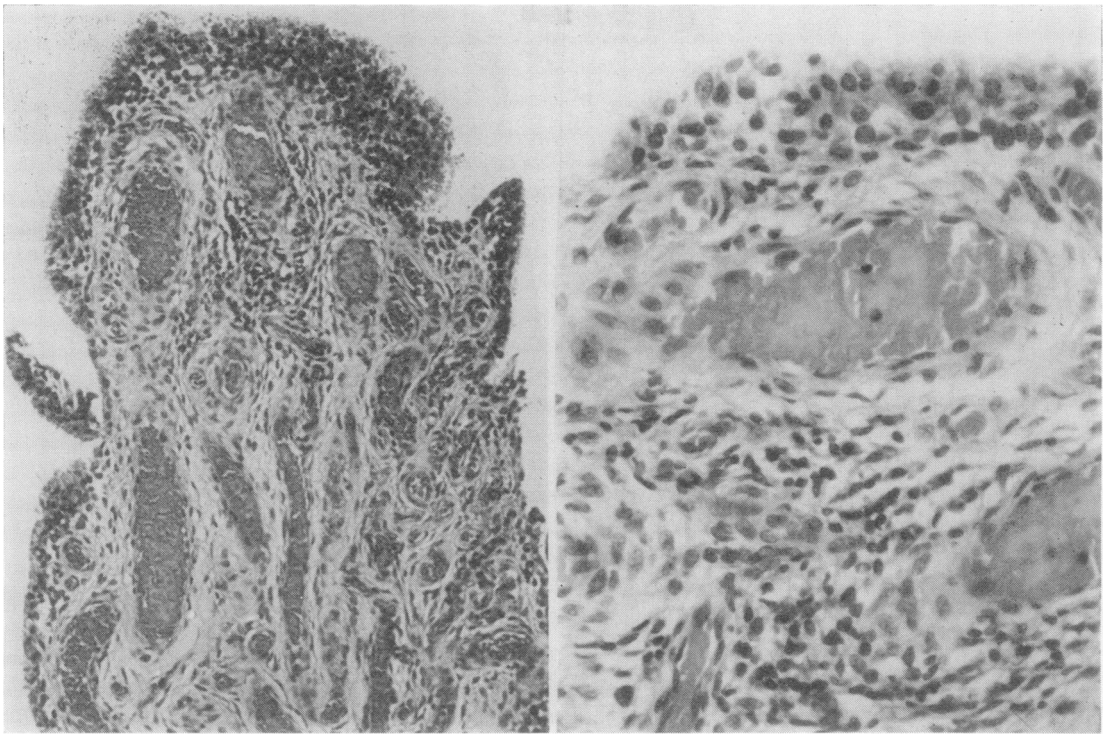

FIG. 2a *Microvillus, showing vascular synovium with a thickened layer of intimal cells and a chronic inflammatory cell infiltrate in the stroma. Haematoxylin and eosin.* × 150.

FIG. 2b *Higher power view of Fig. 2a, showing chronic inflammatory cell infiltrate. Haematoxylin and eosin.* × 420.

for the non-iron containing group, this difference being statistically significant ($P < 0{\cdot}005$). Two of the three patients in whom iron was present in the synovium with normal chelatable iron stores had only recently completed venesection therapy.

It has also been possible to relate the presence of synovial iron to the main parenchymal organ to be involved in haemochromatosis, the liver. In the seventeen patients in whom the relationship could be examined, there was a significant direct relationship between the grading of liver iron and the presence of synovial iron (Fig. 4). One patient with Grade 4 hepatic siderosis who had no synovial iron had both symptoms and radiological evidence of an arthropathy.

Discussion

The present study indicates both the value and limitations of needle biopsy as an investigatory tool for examining the synovium in patients with haemochromatosis. Deposits of iron when present were found mainly in the synovial intimal cells and frequently in the phagocytic cells of the stroma with none lying free. Furthermore, other histological

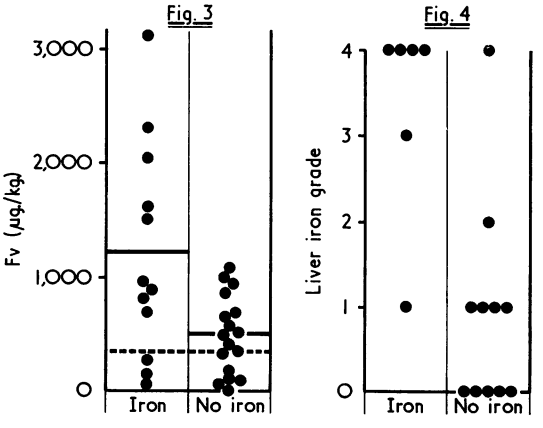

FIG. 3 *Presence or absence of iron in synovium related to extent of body iron stores using differential ferrioxamine test. Two results are included from patients having a repeat study after venesection therapy to bring the chelatable body iron stores to normal. One had synovial iron and the other did not. No change occurred after treatment.*

FIG. 4 *The presence or absence of iron in synovium related to grade of hepatic siderosis.*

abnormalities were found in a significant number of patients. Proliferation of the intimal cells was often marked. This has been a variable feature in past descriptions. Cappell, Hutchinson, and Jowett (1957) described cases of transfusional siderosis in which the synovial membrane was heavily iron laden but was not proliferated in contrast to the one patient with haemochromatosis they examined. Synovial cell proliferation was noted by Kra, Hollingsworth, and Finch (1965) and by Muirden and Senator (1968) in single patients but not by Schumacher (1964) in two patients.

In contrast to the situation in rheumatoid arthritis, villus formation was not seen macroscopically in the autopsy specimens, but microvilli were commonly seen in the biopsies and in all autopsy specimens. The chronic inflammatory cell infiltrate, which was striking in two of our patients, does not seem to have been previously described.

The presence of synovial iron appears to be related to the degree of total body iron overload. We found that iron deposition was often focal in nature in autopsy cases, and this is one possible limitation of needle biopsy which might result overall in an underestimate of the frequency of iron deposition. This would leave unexplained why some patients do not develop an arthropathy. However, there is evidence that factors other than iron deposition may be concerned in the development of arthropathy. Dymock and others (1970) found that five of 31 patients first noted arthritic symptoms during venesection therapy and a further sixteen after completion of therapy. It could even be argued from such evidence that iron exerts a protective effect. An independent effect of age was also shown by these authors, in that patients who developed the first symptoms of haemochromatosis after the age of 50 years were more likely to develop an arthropathy.

Several authors have described patients with synovial iron who had completed venesection therapy (Schumacher, 1964; Kra and others, 1965; Bauer and Jeffries, 1966). In our series there were three patients with synovial iron and normal chelatable body iron stores. It is possible that in some patients the exchange of synovial iron with the labile iron pool is slower than in others, and it is of interest that two of these patients had only recently completed venesection therapy. It would be important to have information concerning the chemical concentration of iron in the synovium of these patients but for technical reasons this proved impossible.

The lack of iron deposition in the articular cartilage in the autopsy cases is in accord with the experience of some authors (Collins, 1951; Schumacher, 1964). However, Sheldon (1935) considered chondrosiderosis a characteristic feature and Muirden and Senator (1968) described iron-staining of the chondrocytes.

Iron deposition in the synovium is common in rheumatoid arthritis but the distribution is different. It is most commonly sited in the vascular stroma just beneath the proliferated synovial cells and in the deeper connective tissue. Whilst the intimal cells may show some iron it is usually small in amount. The iron deposition in rheumatoid arthritis may follow extravasation from vascular granulation tissue. The chelatable iron stores may be raised in up to one-third of patients with rheumatoid arthritis but do not normally reach the levels seen in haemochromatosis (Wardle and Israëls, 1968).

The role of iron in the aetiology of the joint disease of haemochromatosis is suggested by the observation that the characteristic arthropathy may occur in some patients with secondary iron overload (Dymock and others, 1970). Further elucidation of the processes involved will probably come with greater sophistication in the study of biochemical and enzymic abnormalities in joint disease, but there is a need for a prospective study in which serial biopsies are examined at regular intervals in patients with and without the arthropathy of haemochromatosis. In our hands synovial biopsy has not been associated with any morbidity and has caused little discomfort.

Summary

Synovium obtained mainly by needle biopsy has been examined in 27 patients with idiopathic haemochromatosis. Iron deposits in the intimal and phagocytic cells were found in eleven patients. Intimal cell hyperplasia was present in eight patients and villus formation in seven cases. In two patients there was a chronic inflammatory cell infiltrate. The histological features could not be related to the clinical and radiological evidence of arthropathy but the presence of iron was related to the total body iron stores as assessed by the differential ferrioxamine test. There was also a relationship to the severity of hepatic iron deposition and synovial iron was unusual in patients who had completed venesection therapy.

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