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CASE REPORT

RECURRENT UPPER GASTRO-INTESTINAL BLEEDING, DUODENAL AND GASTRIC ULCER AND PELIOSIS HEPATIS IN A PATIENT WITH WALDENSTROM'S MACROGLOBULINEMIA

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SUMMARY

In a patient initially admitted for acute upper gastro-intestinal bleeding from duodenal ulcer, further investigation led to the diagnosis of Waldenstrom's macroglobulinemia. One year later, under Chlorambucil and Oxymetholone therapy, he had a second episode of acute bleeding due to a gastric ulcer of the lesser curvature. Endoscopic biopsies on both lesions demonstrated localizations of the primary disease. A liver biopsy showed extensive peliosis, despite no clinical or biochemical signs of liver disease. Oxymetholone was discontinued and on a second liver biopsy, 18 months later, there was a striking decrease of peliotic lesions. Our case, besides its unusual gastroenterologic features, is the first reported of an association of asymptomatic advanced peliosis hepatis with anabolic steroids in macroglobulinemia. It emphasizes the need for early consideration of this potentially dangerous disease through a careful follow-up of patients under anabolic steroids.

INTRODUCTION

Waldenstrom's macroglobulinemia may occur with several clinical pictures and the presenting signs or symptoms are also multiple (Imhof et al 1959; McCallister et ai 1967; MacKenzie and Fudenberg 1972).

Upper gastrointestinal bleeding is a rather frequent intercurrence in the clinical course of the disease but is very seldom an early sign (Imhof et al 1959; McCallister et al 1967; MacKenzie and Fudenberg 1972; Cristau et al 1972).

Gastroduodenal lesions are also rare in macroglobulinemia, and have been found mostly as surgical or post-mortem findings, essentially of pseudotumoral nature (Cristau et al 1972; Auche et al 1973 and Cline et al 1975).

Peliosis hepatis has been described in patients with consumptive diseases (Zak 1950; Yanoff e Rawson 1964) or under 17 α — alkilated anabolic steroids (Gordon et al 1960; McGiven 1970; Bernstein et al 1971; Groos et al 1974; Bagheri and Boyer 1974; Westaby et al 1977; Paradinas et al 1977) and more recently in recipients of renal transplants under immunosupressive therapy (Degott et al, 1978); as far as we are aware there are no reported cases of association between macroglobulinemia and peliosis hepatis after anabolic steroids therapy. We report here one of such cases.

CASE REPORT

M. N., a white male farmer, 58 years old, was first admitted to our Hospital in January 1974 because of maelena and acute anaemia (Hb 7 gr/dl). On emergency endoscopy a bleeding duodenal ulcer was seen. Physical examination revealed several slightly enlarged lymph nodes but there was no enlarged liver or spleen.

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Significant laboratory findings were: ESR, 150 mm; erythrocytes, 2 510 000 with 2 % reticulocytes; serum proteins: 10,0 g/dl with 3,05 g/dl albumin, 0,79 gr γ — globulin and 3,61 g/100 ml of a monoclonal fraction of fast gamma mobility. On serum and urine immuno-electrophoresis, an IgM-K monoclonal gammopathy was diagnosed with Bence-Jones proteinuria of K type. Serum viscosity, by Hess viscosimeter, was 4,5 (normal: 3-5). The elimination of free light chains and the high serum level of monoclonal protein suggested malignancy of the disease.

A lymph node biopsy showed disappearance of the normal structure, with almost complete replacement of normal cells by abnormal young lymphoid cells with monotonous morphology, a few plasma cells and some intermediate cell types (Fig. 1). In

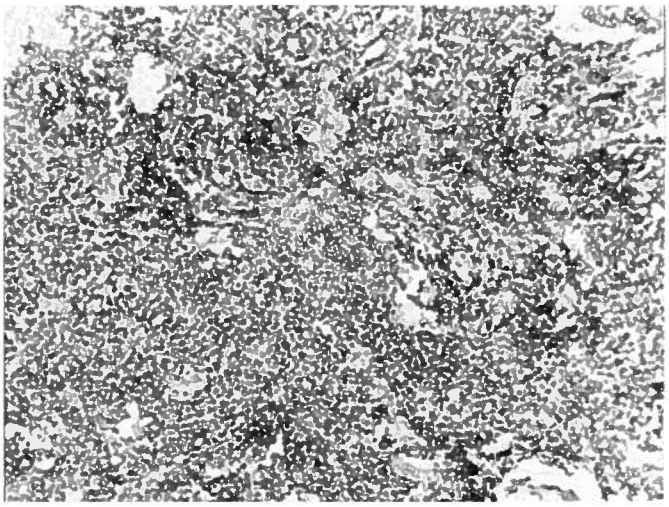

Fig. 1 — *Lymph node: replacement of the normal structure by diffuse infiltration with abnormal lymphoid and plasma cells. H.E.* × *92*

some of them inclusions of PAS positive material could be found. There was invasion of the capsule and peripheral fat. The bone marrow showed few normal cells and dense infiltration by lymphoid and plasma cells. IgM was found within these cells by immunofluorescence. These findings confirmed the diagnosis of Waldenstrom's macroglobulinemia.

Ocular fundus, serum iron (84 μg/100 ml), liver function tests (SAT-15 i.u.; AP-3 U. Bodansky; Bilirubin — 0,2-0,6 mg/dl), coagulation studies and bone X-rays were all normal. Erythrocite autoantibodies were negative.

Two control endoscopies showed complete healing of duodenal ulcer. A biopsy of the mucosa of the duodenal bulb was performed. There were cells similar to those found in the lymph node but mainly of plasmacitoid type.

Despite no further bleeding and a transfusion of 2 units of total blood, there was no improvement in the hemoglobin level and, in March 74, Chlorambucil (4 mg daily) was started. One month later the drug was discontinued for two weeks because of low red cell (2 524 000) and leucocyte (3000) counts. A lower dose was then started (3 mg daily) plus Oxymetholone (100-150 mg daily).

There was good clinical and laboratory recovery with marked reduction of abnormal lymphoid and plasma cell infiltration of bone marrow.

In January 75, the patient was again admitted to our Hospital because of acute anaemia (Hb 6.5 g/dl) and maelena, due to a bleeding gastric ulcer of the upper lesser curvature. Two weeks later, the ulcer was almost completely healed and a biopsy of its border showed the same type of cellular infiltration of the previous duodenal biopsy (Fig. 2).

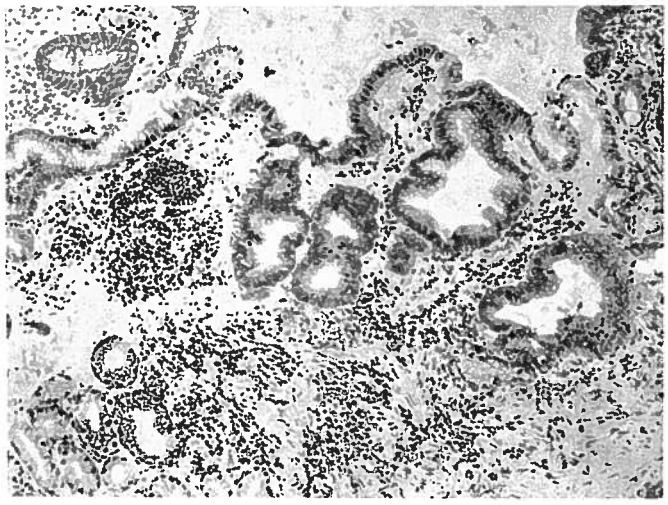

Fig. 2 — *Gastric mucosa: focal infiltration of the corion by abnormal lymphoid and plasma cells H.E.* × *92*

Meanwhile, treatment with Chlorambucil and Oxymetholone (total dose of Oxymetholone 25 gr) had been discontinued since the patient's admission to hospital. A liver biopsy was performed due to persistently low serum albumin. It showed slight enlargement of portal tract with heavy cellular infiltration similar to that described for the other organs (Fig. 3). There were also many large intralobular blood filled cystic spaces, lined by hepatocytes, endothelial cells or a thin coat or reticular fibers; there were focci of sinusoidal dilation of variable degrees — these lesions correspond to a well established peliosis hepatis (Fig. 4). The patient left hospital 3 weeks later on 2 mg of Chlorambucil daily. No further Oxymetholone was given.

He has been followed up since then as an outpatient. In June 76, immunoelectrophoresis showed a total serum protein of 8,1 g/dl with 3,1 g/dl albumin and 2,8 g monoclonal protein IgM. At that time, a 2.nd liver biopsy showed the same cellular infiltration in the portal tracts but peliotic lesions were markedly reduced in number and size (Fig. 5).

The patient is now (June 1979) five years after initial diagnosis in quite good clinical condition and performing regular farm work, on a small dose of Chlorambucil therapy (2 mg daily or in alternate days, according to leucocyte counts). He regained weight (6 kg), and had no further G.I. bleeding or any other complaints, namely hiperviscosity syndrome. Physical examination only discloses some small painless nodes in the left supraclavicular fossa. ESR is 110 mm and actual hemoglobin values vary between 11 and 12 g/dl.

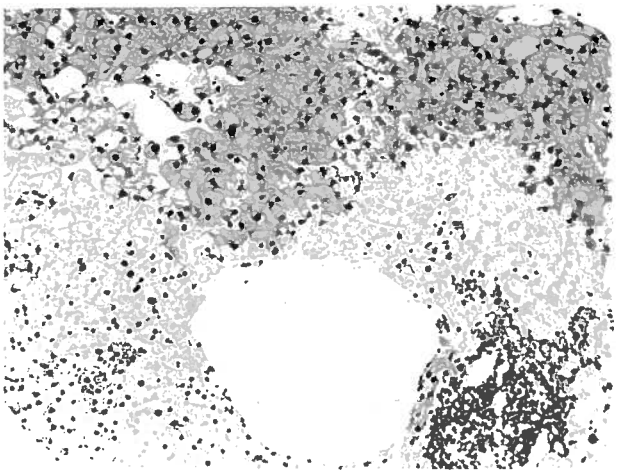

Fig. 3 — *Liver biopsy. Besides the peliotic lesion there is infiltration of the portal tracts by abnormal lymphoid cells. H.E. × 85*

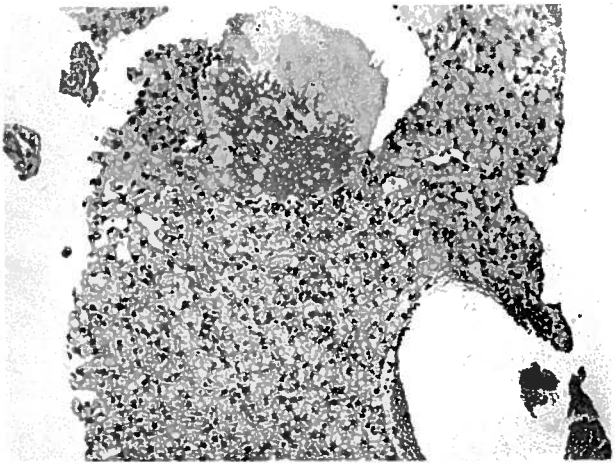

Fig. 4 — *Liver biopsy. Peliosis of parenchymal variety. There are all transitions between dilated sinusoids and irregular blood cysts unlined by endothelium. H.E. × 66*

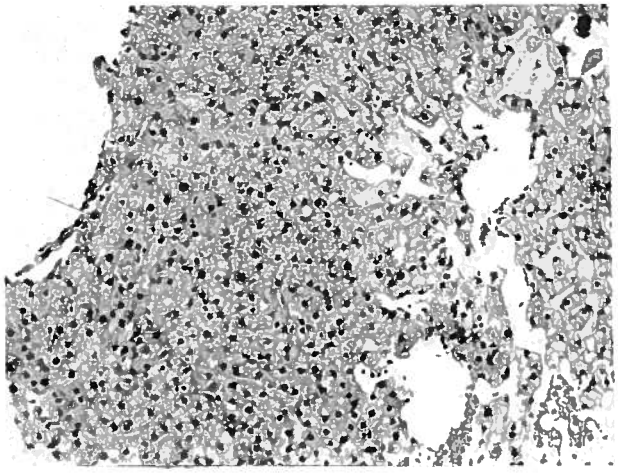

Fig. 5 — *2nd liver biopsy. Peliotic cysts are smaller and less numerous. H.E. × 85*

DISCUSSION

In this case of Waldenstrom's Macroglobulinemia several unusual features deserve special comment:

— The episode of haematemesis is very seldom the initial sign that sends the patient to hospital and leads to the diagnosis of macroglobulinemia, though acute or chronic g.i. blood loss is a rather frequent intercurrence in the previously diagnosed cases (Imhof et al 1959; McCallister et al 1967; McKenzie and Fudenberg 1972; Cristau et al 1972). In a review of 227 cases of Waldenstrom's disease (McCallister et al 1967) only in 10 was g.i. bleeding the first manifestation. Only one of the 40 patients discussed by MacKenzie (1972), had a bleeding episode as the initial sign of the disease. In another case (Cristau et al 1972) massive g.i. bleeding prompted surgical treatment and atypical cells were found both in an active gastric ulcer and in an healed duodenal ulcer.

— Emergency endoscopy, on both episodes, showed two independent sources of bleeding with localizations of the disease.

Later endoscopies showed rapid healing of both lesions. Gastrointestinal localizations of Waldenstrom's disease have been histologically confirmed in 11 published cases: 7 pseudotumours, 2 gastric ulcers, 1 duodenal ulcer and 1 gastric plus duodenal ulcer (Cristau et al 1972; Auche et al 1973; Cline et al 1975). Unlike our case, these lesions were confirmed only on surgical or necropsy specimens, with two exceptions (Auche et al 1973; Cline et al 1975). According to other authors' reports and our own, the occurrence of gastrointestinal lesions and even recurrent episodes of bleeding do not seem to have any deleterious effect in the clinical evolution of the primary disease and should not be a reason for depriving the patient from adequate life-long cythostatic therapy.

— There was the clinically unsuspected association of peliosis hepatis, after oxymetholone therapy and its improvement following withdrawal. Peliosis hepatis was first described in 1861 by Wagner, and the first cases reported were in connection with consumptive systemic diseases like tuberculosis (Zak 1950). Later on, these lesions were described after treatment with anabolic steroids and their potential clinical severity has been emphasized in a review of 7 cases, 6 of which were diagnosed on necropsy specimens (Bagheri and Boyer 1974). So far, only the 17-α — alkylated steroid derivatives have been implicated in the development of peliosis hepatis (Westaby et al 1977; Paradinas et al 1977). In a recent series of 60 patients with high doses of methyltestosterone for transsexuality or impotence (Westaby et al 1977), sinusoidal dilatation was present in 9 cases, 3 of which with microcyst formation, corresponding to early peliosis hepatis. Up to now, at least 28 cases were reported with this complication (Paradinas et al 1977).

In our patient, peliosis hepatis was found in the liver biopsy specimen after several months of oxymetholone therapy and a total dosage of 25 g.

Unlike all the previously reported cases, in this patient there were no hepatomegaly or signs of portal hypertension or liver disfunction, with the exception of the persistently low serum albumin levels. Diagnosis of peliosis hepatis by liver biopsy has been exceedingly rare, except in one series (Degott et al 1978) and this is the first reported case showing a well established pathological condition before the appearance of clinical or biochemical signs of liver disease.

The pathogenesis of this lesion is a subject of controversy (Gordon et al 1960; Yanoff and Rawson 1964; McGiven 1970; Bagheri and Boyer 1974; Westaby et al 1977; Paradinas et al 1977), but in the cases of Westaby et al (1977) and Degott et al

(1978) the hyperplasia and prolapse of hepatocytes into the lumen of centrilobular veins seemed to obstruct the blood flow and could be the main cause of cystic sinusoidal dilatation (Paradinas et al 1977). Furthermore, a firm causal relationship between anabolic steroids and peliosis hepatis has not yet been established and again in our case it can not be clearly demonstrated. To our knowledge there are no reported cases in the literature of association between peliosis hepatis and Waldenstrom's macroglobulinemia, and there is no evidence that haematologic disorders played any role in the development of peliosis. In our patient such an association exists and, even with oxymetholone, macroglobulinemia itself and chlorambucil therapy can not be excluded as additional ethiological factors of the peliotic lesions. Recently, another immunosuppressive agent, azathioprine has been incriminated as a possible cause of peliosis hepatis (Degott et al 1978).

Another feature deserving mention in our case is the histological improvement seen in the control liver biopsy 18 months after discontinuing oxymetholone. It could be a sampling error but this finding is in favour of the suggested reversibility of this severe liver injury (Groos et al 1974) and is a further argument to incriminate oxymetholone as its main ethiological factor. The need of early detection of peliosis hepatis in patients under anabolic steroids needs to be emphasized. Patients receiving immunosuppressants should be eventually regarded in the same way. If long-term therapy is decided in patients with severe systemic diseases, a liver biopsy should be considered early in its course, to support a sound clinical judgement between potentially severe iatrogenic risks (whilst still reversible) and eventual therapeutic benefits. Alternatively, a careful follow-up with liver scans (Paradinas et al 1977; Gordon et al 1960; McGiven 1970; Groos et al 1974) or grey-scale ultrasonography, may offer the possibility of an effective supervision in these patients.

Acknowledgement

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RESUMO

Num doente de 58 anos, internado por melenas e anemia aguda, a endoscopia de urgência revelou úlcera duodenal e a investigação posterior conduziu ao diagnóstico de macroglobulinémia de Waldenström. Um ano depois, sob terapêutica com clorambucil e oximetolona, o doente é internado por novo episódio de hemorragia digestiva por úlcera gástrica da pequena curvatura, diagnosticada na endoscopia urgente. As biópsias endoscópicas de ambas as lesões demonstraram localizações da doença primária. No segundo internamento, a biópsia hepática revelou extensas lesões de peliose sem evidência clínica ou laboratorial de lesão hepatocelular. Uma segunda biópsia hepática, 18 meses depois da suspensão do tratamento com oximetolona, mostrou redução marcada das lesões pelióticas. O nosso caso, para além das suas manifestações clínicas pouco habituais, é o primeiro relatado de peliose hepática associada ao uso de esteróides anabolizantes na macroglobulinémia. Discutem-se os factores patogénicos em causa e as respectivas implicações clínicas, com relevo especial para a necessidade de considerar precocemente o risco de peliose hepática nos doentes sob terapêutica anabolizante prolongada.

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