Granulomatous hepatitis in association with fever and a palmar rash

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ABSTRACT: Secondary syphilis may present without the classical features of the disease and should be considered in patients acutely ill with abnormal liver function tests and a nonspecific pattern on liver biopsy. Secondary syphilis may present in association with granulomatous hepatitis and serological testing should be performed if the etiology of the hepatic granulomas is unclear. While the finding of a disproportionate elevation of alkaline phosphatase relative to serum bilirubin may be a useful pointer towards the diagnosis this pattern is not specific and not consistently observed. The definitive answer to the question of whether syphilitic hepatitis exists awaits the development of comprehensive tests to exclude viral pathogens. *Can J Gastroenterol* 1987;1(1):37-40

Key Words: Granuloma, Hepatitis, Syphilis

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Received for publication May 10, 1987. Accepted June 4, 1987

A 51-YEAR-OLD WOMAN WAS ADMIT-
ted to hospital with headache and fever. She had been well until two weeks prior to admission when she experienced the onset of bifrontal headache, mild photophobia and intermittent nausea. The patient had consulted her family doctor one week before admission and metronidazole was prescribed for symptoms of vaginal discharge thought to be due to trichomonas infection. Three days before admission, fever, rigors and generalized joint stiffness were noted. There was no history of sore throat, skin

Figure 1) Left Mononuclear infiltrate in the portal tracts. Right Noncaseating granuloma

rash or arthritis. She denied the use of intravenous drugs and had never received a blood transfusion.

The patient lived alone having been recently separated from her husband. She drank alcohol rarely and in minimal amounts. The patient was taking thyroxine because of hypothyroidism resulting from a previous partial thyroid resection for hyperthyroidism 15 years previously. There was a history of pneumonia in the distant past and a hysterectomy and bilateral salpingo-oophorectomy had been performed eight years previously for symptoms of pelvic pain; no specific diagnosis was made. Functional inquiry was unremarkable except for a long history of occasional left lower quadrant abdominal pain.

Physical examination revealed temperature of 39°C, irregular pulse of 80 beats/min and blood pressure 130/90 mmHg. The patient was orientated and alert but appeared ill. There was no evidence of skin rash. Examination of the mouth, head and neck was unremarkable. There was no evidence of lymphadenopathy. No meningeal signs were elicited and fundoscopy revealed normal optic discs. The chest was clear to auscultation and heart sounds were normal with no audible murmurs. The liver and spleen were not enlarged. The muscles were not tender and there was no evidence of arthritis. Vaginal examination was not performed.

INVESTIGATIONS

Hemoglobin was 129 g/L, white cell count $4.6 \times 10^9/L$ with 30% polymorphonuclear leukocytes, 26% lymphocytes,

7% monocytes, 2% eosinophils and 35% bands. The erythrocyte sedimentation rate was 93 mm/h. The serum electrolytes, urea nitrogen and creatinine were normal. Examination of the urine revealed no abnormalities.

A chest x-ray showed borderline cardiomegaly but the lung fields were clear. An electrocardiogram showed sinus rhythm with ventricular bigeminy and trigeminy. An echocardiographic examination of the heart showed no evidence of valvular lesions.

The total serum bilirubin was 10.2 mmol/L (normal 2 to 18), aspartate aminotransferase 186 iu/L (normal 8 to 40), lactate dehydrogenase 217 iu/L (normal 100 to 240), alkaline phosphatase 1015 iu/L (normal 30 to 110). Frac-

tation of the alkaline phosphatase showed that 95% was of hepatic origin. The 5' nucleotidase was 155 iu/L (normal 3.2 to 11.6). The prothrombin time was 14 s and the partial thromboplastin time 43 s. Serum protein electrophoresis was performed; total protein was 68 g/L (normal 60 to 80), albumin 33 g/L (normal 35 to 52), alpha-1 globulin 4.5 g/L (normal 1 to 4), alpha-2 globulin 9.4 g/L (normal 4 to 8), beta-globulin 9.4 g/L (normal 6 to 10) and gamma-globulin 11.8 g/L (normal 7 to 16).

An ultrasonographic examination of the liver showed no dilatation of the intra- or extrahepatic bile ducts and no focal abnormalities. An intravenous cholangiogram was attempted but visualization of the bile ducts was not obtained.

Figure 2) Palmar rash suggestive of secondary syphilis

Figure 3) Time course of the biochemical changes in relation to the liver biopsy and commencement of treatment with penicillin. SGOT Aspartate aminotransferase

A Widal test, a slide test for mononucleosis and toxoplasma titres, was within normal limits. The hepatitis B surface antigen test was negative. Cultures of urine and blood gave no growth. Bone marrow aspiration showed no evidence of *Mycobacterium tuberculosis*. Tests for rheumatoid factor and for antibodies against nuclear antigen, reticulin, mitochondria and smooth muscle were negative. A radionuclide scan of the brain was normal. Thyroid scan showed a defect possibly due to previous surgery but thyroid function was biochemically normal.

Twenty-six days after the start of the illness a liver biopsy was performed (Figure 1). The overall architecture of the liver was preserved. The portal areas were infiltrated with lymphocytes and slightly expanded. The bile ducts were normal. Several noncaseating granulomas were seen with no particular distribution. Within the lobules there were numerous focal collections of lymphocytes but little evidence of hepatocellular necrosis. The areas around the central vein were normal. Stains for *M tuberculosis* and *Treponema pallidum* were negative.

On the 29th day of the illness the characteristic rash of secondary syphilis appeared (Figure 2) and subsequently

the FTA-ABS and VDRL were reported to be positive. Although the patient had denied a history of casual sexual contact she now admitted to a brief encounter with a male who had a penile wart or ulcer. High dose intravenous penicillin was started and continued for 10 days. The fever, rash and joint pain became worse on the first day of treatment (Jarisch-Herxheimer reaction) but subsequent resolution of the clinical and laboratory abnormalities occurred. Figure 3 shows the resolution of the liver function abnormalities. The VDRL titre, which was initially positive at 1/256, fell to a negative titre of 1/64.

DISCUSSION

The patient presented with a history suggestive of an acute infectious or inflammatory process. Physical examination and extensive radiological investigation did not reveal an obvious source of sepsis and cultures were negative. The most striking laboratory findings were the abnormal liver function tests and the disproportionately high alkaline phosphatase relative to serum bilirubin. Hepatic ultrasound showed no evidence of biliary obstruction and a subsequent liver biopsy showed portal infiltration, a lobular hepatitis and numerous granulomas.

Hepatic infiltration with granulomas may occur in a variety of illnesses (1,2) but in this setting tuberculosis seemed a strong possibility. However, the chest was clear and the marrow revealed no evidence of mycobacteria. Sarcoidosis was considered but the absence of hilar lymphadenopathy and arthritis argued against this. Hepatic granulomas have been reported in association with connective tissue diseases such as lupus erythematosus (3) but the antinuclear antibodies were negative.

On day 29 of the patient's illness a rash appeared with the rather characteristic distribution of secondary syphilis. Syphilis had not been considered on presentation because of the absence of mucous membrane lesions, lymphadenopathy or a rash. Furthermore, the patient initially denied a history of casual sexual contact.

The high titre VDRL and FTA-ABS, the Jarisch-Herxheimer reaction and a

subsequent fall in titre after treatment with penicillin confirmed the clinical diagnosis. Further support for the diagnosis of secondary syphilis was given by the patient's revelation of casual sexual contact with a male who had a penile lesion.

Clinically evident hepatic involvement in secondary syphilis is not common. Hahn (4), in a remarkable study of an estimated 10,000 cases of early syphilis, reported that jaundice occurred in only 0.05%. However, biochemical evidence of hepatic involvement, as in the present case, has been reported to occur in 10 to 91% of patients with the disease (5,6).

A disproportionate elevation of alkaline phosphatase relative to the serum bilirubin is occasionally observed in this condition (7). A similar biochemical pattern may be seen in granulomatous hepatitis (8) but in neither condition is this a consistent finding (5,6). The reasons for this biochemical pattern are unclear.

Even if hepatic involvement is present the biopsy findings can be rather nonspecific and very variable. The problem of identifying a specific histological pattern is compounded by the possibility of simultaneous infection with viral agents in a population at risk for both syphilis and viral hepatitis. Not infrequently an ulcerating chancre may be present in the rectum (7). It is possible that at least some of the nonspecific alterations in hepatic morphology may be related to this. Spirochetes, as in this case, are rarely found in the liver but this may represent difficulties in methodology. It has been postulated that the hepatic damage is mediated by immune complexes (9).

The portal areas are almost invariably infiltrated by mononuclear cells and occasionally by polymorphonuclear leukocytes. Pericholangitis may be observed (7) but cholestasis is uncommon. The hepatic inflammation may predominate around the central veins occasionally in association with perivenular fibrosis (5). Kupffer cell proliferation may be prominent (6). Hepatocellular necrosis between portal areas and central vein has been reported (10). Granulomatous infiltration, as in this patient, may occur (11) but this is not common. The most consistent pattern of parenchymal involvement appears to be focal collections of

mononuclear cells with little hepatocellular necrosis.

The wide variation in clinical, biochemical and histological features, and the failure to exclude other pathogens has led to a continuing scepticism as to whether the hepatic damage observed in secondary syphilis is related to the spirochetes (12). In the present case, alcohol intake was minimal, metronidazole has not been reported to cause hepatic granulomas and screening for hepatitis B was negative. We did not test for hepatitis A but a slide test for Epstein-Barr virus was negative. We cannot exclude the possibility of non-A, non-B hepatitis but neither the biochemical nor the histologic features were particularly suggestive of a viral etiology.

The resolution of abnormal liver function tests began before treatment was started. This has previously been reported (13) and may be illustrative of the tendency for secondary syphilis to resolve to a latent phase.

The Jarisch-Herxheimer reaction is a feature of the treatment of syphilis. In the case reported by Young et al (13) the Jarisch-Herxheimer reaction was accompanied by both clinical and biochemical exacerbation. A deterioration in liver enzymes was not seen in the present case.

ACKNOWLEDGEMENTS: The authors acknowledge the assistance of Drs P Fernandez, I Bowmer and S Chittal in the presentation of this manuscript.

L'hépatite syphilitique: Existe-t-il ou non ?

LE SECOND DEGRÉ DE LA SYPHILIS PEUT SE PRÉSENTER SANS LES PARTICULARITÉS classiques de la maladie et chez les patients sévèrement malades avec une fonction anormale des tests du foie et un modèle non précis de la biopsie du foie, la diagnose de la syphilis devrait être considérée. Le second degré de la syphilis peut se présenter en association avec l'hépatite granulomateuse et le test sérologique devrait être exécuté si l'étiologie de l'hépatite granulomateuse n'est pas claire. Quoique la constatation disproportionnée de l'élévation de l'alkaline phosphatase relatif au sérum bilirubine serait un indice profitable vers le diagnostique, ce modèle n'est pas spécifique et pas toujours observé régulièrement. La réponse définitive à la question si l'hépatite syphilitique existe ou non attend le développement des tests compréhensifs pour exclure tout virus qui sont susceptibles de donner l'hépatite.

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