

Tertiary syphilis presenting as hepatic bull's eye lesions

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Abstract

We report a rare case of tertiary syphilis (hepatic gummata, asymptomatic neurosyphilis and iridocyclitis) in a 47 year old female patient. Our patient suffered from a troubled sight, pain in the right hypochondrium, one enlarged submandibular lymph node, an elevated sedimentation rate, disturbed liver tests and two hepatic lesions upon abdominal computed tomography. The diagnosis was based upon a liver biopsy and a positive *Treponema Pallidum* haemagglutination test. The patient was treated with doxycyclin. After treatment the sedimentation rate and liver tests normalised and the hepatic lesions disappeared leaving a small 'scar' on CT-scan ; at the end she still complained of a decreased sight. We conclude that syphilitic gummata of the liver have a favourable prognosis when the diagnosis is made early. One has to differentiate with hepatic abscesses, primary tumours and metastases (*Acta gastroenterol. belg.*, 2005, 68, 435-439).

Key words : bull's eye, syphilis, liver, gummatous, cirrhosis, granulomatous, hepatitis, iridocyclitis, metastasis, hepar lobatum.

Introduction

Syphilis is caused by the spirochete *Treponema Pallidum*, which spreads itself via the blood and lymphatic vessels to any organ. The transmission is usually sexual. Other types of transmission are blood transfusion or congenital (in utero or via the birth channel). The incubation time is three weeks. The primary stage appears 2 until 6 weeks after the infection and consists of one painless papule (= chancre), attended with regional lymphadenopathy. The secondary stage appears 6 till 8 weeks after the healing of the primary chancre and consists of diffuse mucocutaneous lesions, attended with generalised lymphadenopathy. Subsequently there's a subclinical latent period during which a specific treponemal antibody test is positive. In one third of the untreated patients, a tertiary stage follows, which is marked by a slowly progressive inflammation of any organ. To achieve the diagnosis, serological tests should be realized : for the purpose of screening a nontreponemal or reaginic test, e.g. Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) test, is used ; to confirm the diagnosis a specific treponemal antibody test is used, e.g. a fluorescent treponemal antibody absorption (FTA-abs) test and a TPHA-test.

The treatment depends on the stage and consists among other of penicillin G, doxycyclin, cephalosporin.

Case report

At the end of January 2000 a 47 year old woman went through an infectious syndrome with fever (39°C) that lasted one week. She had a past history of arterial hypertension, appendectomy, arthrosis and smoking. At the end of February 2000 she spent a week on Mauritius. Since March 2000 she presented with general complaints of fatigue, myalgia, arthralgia and anorexia with a weight loss of 20 kg without following a diet. An electromyography (EMG) of the upper and lower limbs was normal. In April 2000 she presented with pronounced pain in the right hypochondrium, radiating towards the right shoulder. At the end of May 2000 she noticed enlarged lymph nodes in the cervical region. In June 2000 she was treated by an ophthalmologist because of an acute iridocyclitis with a troubled sight. In July 2000 she was referred at the consultation of gastroenterology because of one enlarged lymph node and a suspected cytomegalovirus (CMV) infection with hepatitis on blood testing.

There was no history of contact with cats neither with other animals. The stool pattern was unchanged. When asked, patient admitted unprotected sexual intercourse with two males in the middle of January 2000.

Physical examination showed one enlarged lymph node in the right submandibular region ; the other regions were negative. Splenomegaly was also present.

On the basis of the available laboratory results, the tentative diagnosis was a CMV-infection with hepatitis, splenomegaly and an enlarged adenopathy. Additional examinations (blood tests, iconography) were planned to exclude e.g. haematological malignancies (lymphoma). The enlarged submandibular lymph node was resected and histological examination performed : there was a florid chronic lymphadenitis, without arguments for malignancy ; the capsule and the adjacent tissue was infiltrated with plasma cells ; these plasma cells were found around smaller capillaries and veins, and in one

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smaller vein they were also noticed in the vessel wall ; the arterioles and small arteries were normal.

The important laboratory results were : erythrocyte sedimentation rate after one hour 64 mm ; C-reactive protein (CRP) 1.2 mg/dl (normal 0- 0.7) ; lupus anticoagulants negative ; cold agglutinins titre 1/32 (normal < 1/32) ; strong elevation of the gammaglobulines in the protein electrophoresis ; immunoglobulin G (IgG) class antibodies 2330 mg/dl (normal 694-1618) ; immunoglobulin M (IgM) class antibodies 305 mg/dl (normal 60-263) ; direct bilirubin 0.5 mg/dl (normal 0.1-0.4) ; alkaline phosphatase (ALP) 235 U/l (normal 38-126) ; gamma-glutamyltranspeptidase (gamma-GT) 135 U/l (normal 12-43) ; total cholesterol 270 mg/dl (normal 140-220) ; total cortisol 24.6 µg/dl (normal 6-30, in the morning) ; cancer antigen 19.9 (CA 19.9) 7.3 U/ml (normal 0-37) ; carcinoembryonic antigen (CEA) 0.6 ng/ml (normal 0-5) ; alpha-fetoprotein 1.63 ng/ml (normal 0-10) ; anti-Epstein-Barr virus (EBV) immunoglobulin G (IgG) antibodies 88 U/ml and immunoglobulin M (IgM) negative ; anti-CMV IgG 1478 IU/ml (normal < 15) and anti-CMV IgM positive ; anti-Bartonella henselae IgG positive ; anti-toxoplasma IgG and IgM negative ; anti-Mycoplasma pneumoniae antibodies titre 1/80 (normal < 1/80) ; antinuclear antibodies (ANA) titre 1/160 (normal < 1/80) ; anti-histones and anti-extractable nuclear antigens (ENA) antibodies negative ; antimitochondrial antibodies (AMA) titre 1/160 (normal < 1/10) ; coeruloplasmin 47 mg/dl (normal 22-61) ; serum angiotensin converting enzyme (SACE) 34 U/l (normal 8-52). Urinary sediment and culture were negative.

An electrocardiogram (ECG), X-ray of the chest and the abdomen and a pulmonary function were normal.

A duplex ultrasonography of the abdomen (Fig. 1) revealed a splenomegaly of 15 cm and a round nodule of 3 cm in the right liver lobe with vascularisation of the borders of the nodule and a blood vessel crossing the nodule. A CT-scan of the abdomen (Fig. 2) confirmed the splenomegaly and revealed two bull's eye lesions in the right liver lobe, which measured 4.8 and 2.5 cm. The lesions in the liver were suspicious of metastasis, and a



Fig. 1. — Duplex ultrasonography of the liver : nodule of 3 cm in the right liver lobe.

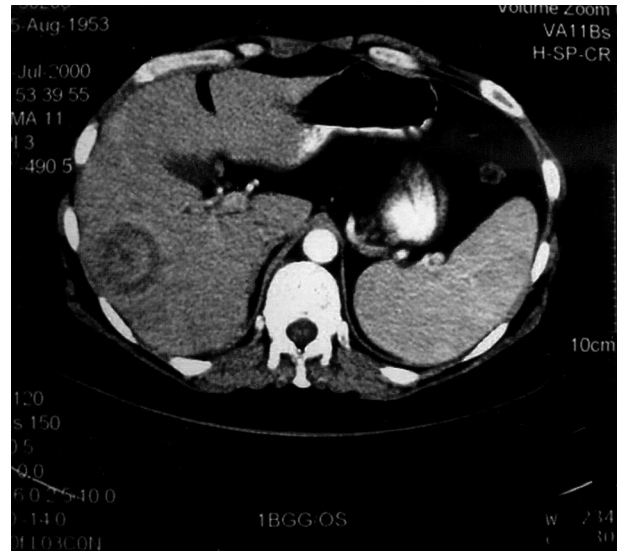


Fig. 2. — CT-scan of the abdomen : 'bull's eye' lesion in the right liver lobe, measuring 4.8 by 2.5 cm.

search for a primary tumour was initiated : ultrasonography and mammography of the breasts, CT-scan of the chest, gastroscopy and colonoscopy were normal.

At last a CT-guided biopsy in the largest hepatic bull's eye lesion was performed. Histological examination showed normal liver tissue, progressing into fibrous liver tissue ; granuloma were found in both normal and fibrous liver tissue ; the granulomatous lesions consisted of multinucleated giant cells, epithelioid cells and lymphocytes ; a dense infiltration of lymphocytes with some sparse neutrophilic granulocytes was seen in the fibrous tissue ; in conclusion there was a strong chronic granulomatous hepatitis ; a Ziehl-Neelsen staining didn't show acid-proof bacilli ; there were no arguments for malignancy, haemangioma or focal nodular hyperplasia ; immunohistological staining of the bile ducts showed that they were well conserved and could not reveal neocholangiolar proliferation, which made primary biliary cirrhosis very unlikely ; a specific staining could exclude a Langerhans cell granulomatosis.

At the time the liver biopsy had been done, the final blood results were disclosed : RPR titre 1/128, TPHA titre > 1/40960, FTA-abs titre >1/400.

Because of these findings, a lumbar puncture was performed. Examination of the cerebrospinal fluid revealed 96 mononuclear cells/mm³ ; 16 polynuclear cells/mm³ ; red blood cell (RBC) count of 32/mm³ ; glucose 49 mg/dl (normal 40-80) ; protein 61 mg/dl (12-60) ; lactic dehydrogenase (LDH) 160 U/l ; RPR titre 1/1, TPHA titre 1/256, FTA-abs positive.

The diagnosis of tertiary syphilis was achieved, with presence of gummata in the liver, iridocyclitis and asymptomatic neurosyphilis. The unprotected sexual contacts had presumably been the source of the infection. A chancre was not noticed by the patient, but such a lesion is painless and moreover localised on a less vis-



Fig. 3.— CT-scan of the abdomen 6 months after treatment : a small hypodense lesion ('scar') with a diameter of 1.7 cm in the right liver lobe.

ible region. Subsequently the patient went through the secondary stage of syphilis, after which she evaluated to the tertiary, late stage.

She was treated with doxycyclin 200 mg twice a day orally during three weeks.

In January 2001 the patient went for a control consultation. In comparison with the period before the syphilitic infection, the sight was strongly reduced : she had a diminished visual acuity. On clinical examination no hepatosplenomegaly could be discovered and there were no enlarged lymph nodes. The laboratory results showed a normal sedimentation rate and a positive RPR (titre 1/8) and TPHA (titre 1/1250). A control CT-scan of the liver (Fig. 3) showed only a small hypodense lesion with a diameter of 1.7 cm in the right liver lobe, which has been considered as a remainder lesion or scar ; there were no other hepatic lesions.

Discussion

Syphilis ('the great imitator') is caused by the spirochete *Treponema Pallidum*. The infection occurs through an intact mucosa or through a chafed skin. In the course of hours or days the spirochete disseminates via the blood and lymphatic vessels to any organ, inclusively the central nervous system. The infectious dose varies individually. For a rabbit, an inoculum of four spirochetes is sufficient, which divide every 30 to 33 hours. To become a clinical lesion, a concentration of 107 micro-organisms per gram of tissue is required. The transmission is usually sexual. The patient is most contagious in an early stage : he can't spread the disease anymore four years after the infection. Other ways of transmission are blood transfusion or congenital (in utero or via the birth channel). The incubation time is on average 21 days, but can vary from 9 till 90 days.

The primary stage consists of one painless papule (= primary chancre) on the site of inoculation ; mostly the external genitals (the penis and the labia), the anal canal,

the rectum, the cervix or the mouth. Multiple chancres are found in case of a human immunodeficiency (HIV)-infection. The basis is smooth and the borders are elevated and hard and have a cartilaginous consistency. Enlargement of regional lymph nodes (firm, nonsuppurative, painless) accompanies the primary lesion. The chancre heals within 3 to 6 weeks (range, 1 to 12 weeks).

The secondary stage begins 2 to 8 weeks after the appearance of a chancre. In this stage a diffuse, non-itchy, maculopapulous erythematous rash is seen on the back, the arms, the palms of the hand, the soles of the feet, with a morbilliform eruption on the trunk (1, 2, 3, 4). A non-itchy rash is also described all over the body, except on the palms of the hand and the soles of the feet (5). Perianal and anorectal lesions are seen, especially in homosexual men : anal condyloma and ulcers on the penis (1, 2, 6, 7). If hair follicles are involved, bald spots and a loss of the beard and eyebrows are seen temporarily. The secondary stage is attended with generalised, multiple, moderately enlarged, hard, painless lymphadenopathy, especially inguinal, but also in the cervical, the axillary and the epitrochlear regions (the latter should always suggest the diagnosis of syphilis) (1, 3, 4, 7, 8). Constitutional symptoms appear, like anorexia, weight loss, fever, fatigue and asthenia. Virtually any organ can be involved : the central nervous system (with headaches, meningismus, meningitis, cranial nerve involvement), glomerulonephritis, hepatitis, gastrointestinal ulcer, anterior ileitis, sinusitis, posterities, peristaltic.

Following the secondary stage, there can be a latent period with a subclinical course, but with a positive specific treponemal antibody test. The first 4 years are designated as 'early latent syphilis' during which infectious relapses can occur.

One third of the untreated patients develop a tertiary stage, which is marked by a slowly progressive inflammation of any organ. Generally it is subdivided in neurosyphilis, cardiovascular syphilis, and gummatous syphilis (spleen, bone, skin ...) (1, 2, 4, 5, 7, 9, 10, 11).

The liver can be involved in any stage (congenital, secondary and tertiary syphilis, less frequently in primary syphilis) (1, 5, 12, 13). Hepatomegaly is described (4, 7, 14, 15). Some patients present with epigastric pain, pain in the right upper quadrant or a sensation of pressure in the abdomen.

Most of the articles deal with hepatitis in secondary syphilis. There's a liver dysfunction with a disproportional increase of the alkaline phosphatases till ten times the normal value (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14). There's a gamma-GT-elevation (6, 7, 8, 9, 10, 14). The transaminases are elevated or normal according to the author (2, 4, 5, 13, 14) : aspartate aminotransferase (AST) - and alanine aminotransferase (ALT)-elevation (6, 11, 14) ; AST and ALT are normal (4, 7, 10) ; AST-elevation without ALT-elevation (5) ; slight elevation of ALT without AST-elevation ; ALT would be the most

sensitive test (13). Bilirubin is normal (3, 4, 6, 7, 14) or slightly elevated according to the author (1, 5, 8, 11). Clinically apparent jaundice is rare. The start of the hepatitis goes together with the rash in the secondary stage of syphilis (3).

The positive anti-CMV IgM is most likely due to stimulation of the immune system in early syphilis, leading to formation of several immunoglobulins, and as such imitating an acute CMV infection. This phenomenon also explains the slight elevation of ANA titre.

Histologically (liver biopsy) four types of lesions are described in secondary syphilis (any or all types may be present concurrently) :

in 90% of the cases there is inflammation with a mononuclear inflammatory infiltrate, consisting of lymphocytes, plasmocytes, monocytes, histiocytes and granulocytes, found in the portal and periportal space, around the central veins and the bile ducts ; less frequently a polymorphonuclear infiltrate (1, 2, 4, 5, 6, 7, 10, 13, 14)

- in 60% of the cases there's a focal intralobular liver cell necrosis, near the portal spaces and around the centrilobular vein, sometimes associated with an inflammatory infiltrate ; there can be a thickened wall of the centrilobular vein with fibrinous deposits ; Kupffer cell hyperplasia may be present (2, 4, 5, 6, 7, 10, 13)
- a mild granulomatous hepatitis with epithelioid cells and giant cells in the portal tract and liver lobules ; these appear isolated, or associated with inflammatory or necrotic lesions (2, 4, 6, 7, 10)
- finally a dilatation of the bile ducts is seen with centrilobular cholestasis with macrovesicular fatty degeneration ; this cholestasis is completely reversible after treatment (4, 5, 13, 14).

Treponemes are usually hard to find : sometimes in the focuses of necrosis, in the endothelial cells of the sinusoids and in the spaces of Disse.

A raised incidence of cirrhosis (14) has been mentioned, probably due to unknown viral hepatitis, to chronic alcohol abuse or to arsenotherapy for syphilis. In general, syphilis does not lead to cirrhosis, unless in cases of congenital and untreated long standing tertiary syphilis (1, 4, 13). In the tertiary stage of syphilis there's fibrosis with formation of gummata : granulomatous lesions with a caseous, rubbery, grey-white necrosis, which appear solitary or multiple. The healing of such gummata leads to superficial scars, which, if they are multiple and localised deeply, lead to cirrhosis and formation of a hepar lobatum (2, 9, 16, 17).

Are their typical lesions on imaging of the liver ? An ultrasound of the abdomen can be normal (4, 5), can show normal bile ducts (4), confirm the hepatosplenomegaly (4, 7), or reveal multiple echo-poor structures (9) or hypoechodense nodules of 10 till 25 cm in size (10). A CT-scan also confirms the presence of hepatomegaly and shows sometimes small punctiform

calcifications in the liver (17). In the latter case, the differential diagnosis should be made with other diseases that are associated with postinflammatory hepatic calcifications : tuberculosis, brucellosis, histoplasmosis, hydatid disease, abscesses, primary liver tumours (fibrolamellar hepatocellular carcinoma, cholangiocarcinoma, haemangioendothelioma, cavernous haemangioma), metastatic tumours (adenocarcinoma of the colon, stomach, pancreas, breast and ovarian serous cystadenocarcinoma), congenital and acquired nonparasitic cysts, old haematomas and intrabiliary calculi. In our case, multiple bull's eye lesions were found, with on CT a central hypodense area, surrounded by a hyperdense rim, at last encompassed with a hypodense rim. These three distinct layers are illustrated by histological sections of a fine-needle aspiration biopsy of a gumma in the liver, which showed an area of acellular necrosis surrounded by a dense fibrous wall with adjacent chronic lymphocytic, plasmocytic and histiocytic inflammation and some epithelioid and giant cell granulomas (10).

The treatment depends on the stage. In early syphilis (primary, secondary) benzathine/procaine penicillin intramuscularly (IM) is used, alone or with an oral regimen of a second antibiotic ; doxycyclin is used in case of allergy to penicillin. In tertiary syphilis multiple treatment schemes are available : e.g. doxycyclin orally for three to four weeks ; penicillin G intravenously for ten days or ceftriaxone intravenously for fourteen days. After initiating antibiotic treatment a Jarisch-Herxheimer reaction can develop : a systemic reaction which consists in the sudden appearance of fever and chills as a result of the release of a heat resistant pyrogen by the spirochetes (5). This reaction is self-limiting and can be treated with acetylsalicylic acid or prednisolone.

In conclusion, as the incidence of syphilis is rising, one should always think of syphilis in the differential diagnosis of hepatitis or hepatic lesions of unknown origin. If therapy is initiated early, the outcome is excellent.

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