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Review paper

Syphilitic hepatitis

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Abstract

Syphilis is a sexually transmitted multisystemic disease known as "the great imitator" due to its variable presentations. Despite being preventable and curable, it still constitutes a major health problem. Hepatic manifestation of syphilis is usually mild cholestatic liver injury but in very rare cases can become fulminant. Moreover, syphilitic hepatitis, known for several decades, is considered rare but is probably under-diagnosed. Given the significant morbidity associated with a missed diagnosis, syphilitic hepatitis should be taken into account as an element of differential diagnosis in patients with unexplained elevation of liver enzymes.

Key words: syphilitic, hepatitis, syphilis.

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Introduction

Syphilis, also known as lues, is a chronic systemic infection caused by the spirochete *Treponema pallidum*. This disease has always had a huge impact not only on the individual, his or her physical and mental condition, but also on public health. Spirochete pallidus infection is transmitted between people mainly sexually during oral, anal or vaginal sex, but also through direct contact of genital organs. Rarely, infection occurs through the placenta, damaged skin, mucous membranes and blood. The natural course of the disease varies, ranging from early syphilis to late syphilis in the absence of treatment [1, 2].

Over time, the infection develops, attacking multiple organs and systems, including the liver, with serious consequences. For this reason, syphilis is also well known as "the great imitator" as it can affect any organ of the body and mimic other infectious and non-infectious conditions. Syphilitic hepatitis, also called "luetic jaundice", is a rare manifestation, being the consequence of bacteria dissemination to the liver. It was reported for the first time in the literature by Harn in 1943 [3]. The local inflammatory response elicited by *Treponema pallidum* is the cause of all clinical manifestations of syphilis; however, the precise mechanisms by which the bacterium leads to liver damage are unclear [4, 5]. Moreover, as *Treponema pallidum* is not a hepatotropic bacterium, liver involvement in the course of the disease can be easily misdiagnosed. Generally a mild disease, very rarely, syphilitic hepatitis can result in fulminant liver failure, as in the case of a patient who required a liver transplantation [6]. One described case of syphilitic liver failure resulted in death [7].

Patients with syphilis may experience symptoms depending on the stage of infection. The course of the disease is also possible with only serological indicators of infection detectable in laboratory tests, but without clinical symptoms (i.e. latent syphilis). However, in some infected people, full-blown disease (overt syphilis) is observed. We talk about early syphilis when the infection lasts no longer than 2 years, and late syphilis when the infection lasts longer than 2 years [8]. Liver involvement in the course of syphilis can be observed in any phase of the disease. A systematic review carried out by Huang *et al*., including 144 patients, revealed that 89% of cases developed during early syphilis and only 6% during late stages [1].

The greatest risk of infection transmission occurs in the early stages. Although it is believed that people around the age of twenty are most often infected, this

trend has not been observed in recent years, especially in people under 25 years of age [9]. Syphilis infection can often be associated with other sexually transmitted diseases. They may also be accompanied by an increased risk of HIV transmission. Syphilis often leads to serious complications in HIV-infected patients; therefore syphilitic hepatitis is considered an HIV-related disease [10].

The greatest risk of infection concerns men infected with HIV who have sexual contact with men (MSM), partners of people infected with *Treponema pallidum*, and people who have unprotected sex with multiple sexual partners [11]. It is postulated that the cholestatic pattern of liver injury seen in the course of syphilitic hepatitis may be due to infection via receptive anal intercourse with subsequent migration of bacteria to the portal circulation and infiltration of bile ducts causing pericholangial inflammation. This is indirectly supported by evidence showing that most syphilitic hepatitis occurs in HIV-positive MSM with syphilitic proctitis [12].

Epidemiology

Registration of syphilis cases is mandatory in most countries of the world. Its spread is influenced by economic, social and moral conditions. The incidence of syphilis was high after World War II. In Europe and the USA, even several hundred cases per 100,000 were registered at that time. After the introduction of penicillin into therapy, the incidence of syphilis decreased significantly. In Poland, this disease has been recorded since 1948. The incidence of early syphilis reached 230 cases per 100,000 inhabitants per year and gradually decreased to 5-7 cases per 100,000 inhabitants per year in 1991-1993, to reach 1.9 in 2020 per 100 thousand people. The most cases were recorded in people aged 30-34 (20.7%) and in men (86.9%). Most often, new cases are reported among MSM – 42%. A similar trend is observed in other regions of the world and is due to the greater mobility of this population and a particular tendency to engage in sexual life and related risky behaviors. As a result of the reorganization carried out in 1998, there was a significant reduction in the number of serological tests for syphilis performed in Poland. Therefore, it cannot be ruled out that the decline in the number of registered cases is at least partly a consequence of this, especially since syphilis treatment is increasingly carried out in private physicians' offices, which ensure greater discretion and, consequently, no reporting of diagnosed cases for registration [10, 13, 14]. Syphilitic hepatitis is a rare clinical diagnosis, with an incidence ranging from 0.25% to 3% [4, 15].

Clinical picture

Congenital syphilitic hepatitis

Congenital syphilis is a disease transmitted through the placenta from mother to child. The likelihood of a child getting sick depends on the severity and stage of the disease in the mother. The most dangerous for the baby is early maternal syphilis, in which the risk of infection is 70-100%. It decreases in latent syphilis to 40%, and is lowest in late syphilis, where it is 10%. Early maternal treatment can prevent fetal infection and complications of syphilis.

Late congenital syphilis, if left untreated, develops within the first 2 years of life. Initially, it does not cause any disturbing symptoms, but over time it can be diagnosed based on:

- involvement of the auditory nerve leading to deafness, which initially manifests itself as tinnitus and dizziness,
- symptoms of the nervous and circulatory systems,
- deformation and damage of teeth,
- pain and watery eyes, accompanied by photophobia, as symptoms of interstitial keratitis, which may lead to blindness,
- exudative arthritis, especially of the knees.

At this stage of the disease, signs of liver damage may also appear, manifesting as jaundice and increased transaminase activity. Congenital syphilis can only be diagnosed in an affected infant by confirming the presence of the spirochete in placental samples or other autopsy material. Liver dysfunction often worsens during treatment for syphilis in infants, as may be indicated by serial measurement of indicator enzymes [10, 16-19].

Congenital hepatic syphilis usually leads to the death of the fetus in the mother's womb or shortly after birth due to serious organic changes in the liver and other organs. The lack of detoxification ability accompanied by fever and pain leads to insomnia and the child's exhaustion. In other cases, death occurs due to liver cirrhosis, biliary scarring, and cholemia, which worsen as the disease progresses. Physical examination reveals enlargement of the liver and spleen and jaundice, accompanied by an increase in transaminase activity, usually with aspartate predominance. Histological examination of liver tissues reveals fibrosis, which may lead to cirrhosis, cholestasis, extramedullary hematopoietic lesions, and in some cases, features of giant cell hepatitis. Symptoms of early congenital syphilis appear by the age of 24 months. The first symptoms may appear soon after birth, but most often appear between the 2nd and 10th week of life. Initially, the child

may have nasal obstruction, sometimes with bone deformation caused by residual secretions. Another feature of congenital syphilis is raised frontal and jaw bones. Various types of inflammatory changes are observed in the cartilage and bone space, and the epiphyses of long bones are damaged. Other early symptoms of congenital syphilis may include: enlarged lymph nodes, anemia, the so-called parrot scar (formed after cracks around the anus and mouth), contractures of the limbs limiting their mobility, and skin lesions on the hands and feet [9].

Acquired syphilitic hepatitis

Liver damage in acquired syphilis is relatively rare [20-23]. Acquired syphilis is divided into early and late syphilis based on its duration. Early syphilis should be diagnosed when the infection lasts up to 2 years, and late syphilis when it lasts longer than 2 years.

Early acquired syphilis

Liver dysfunction caused by *Treponema pallidum* does not usually lead to jaundice, but is associated with increased transaminase activity. Unfortunately, in the differential diagnosis of liver diseases, this spirochete is rarely considered as the etiological factor of hepatocyte damage. The incidence of syphilitic hepatitis is unknown, and tests for it are very rarely performed in patients with damage to the liver parenchyma. Initial symptoms of syphilitic hepatitis may include:

- malaise, feeling of heaviness and pain in the right hypochondrium, fever with chills, nausea, vomiting, anorexia, itching,
- liver enlargement (4-5 cm) with possible pain on palpation,
- in the initial phase of the disease, jaundice appears only as a result of obstruction of the bile ducts,
- the activity of aspartate and alanine aminotransferase is increased, as well as gamma-glutamyltranspeptidase and alkaline phosphatase.

The diagnosis is usually made based on the results of serological tests for syphilis, but other causes of liver damage and biliary tract diseases must be excluded. The use of etiotropic treatment causes rapid resolution of clinical symptoms and abnormalities in laboratory test results.

Later in the course of the disease, patients usually report pain in the right hypochondrium and upper abdomen, which is crampy in nature. Pain may appear at the beginning of the disease and persist or even intensify throughout its course. The body temperature is normal or rises above 38°C, and the fever curve is irregular. An increase in body temperature is often associated with chills and is usually associated with increased inflammation in the liver. If jaundice occurs, it is a consequence of mechanical obstruction of the bile ducts. In untreated cases, disease progression leading to the development of liver cirrhosis is manifested by portal hypertension, ascites and encephalopathy. The blood morphological picture is slightly changed. Only in severe cases do we observe anemia and leukopenia. Syphilitic hepatitis should be differentiated from hepatitis of other etiology, gallstones, abdominal cancer, malaria, cirrhosis and other liver diseases. Co-infection with HIV, HBV or HCV is common in people infected with spirochetes, especially in MSM. Therefore, it should be remembered that in the case of co-infection, the clinical symptoms and laboratory features of liver damage may be complex, which obviously complicates diagnosis [7, 20, 21, 24-28].

Late acquired syphilis

Late syphilis develops in only 10% of cases of untreated early syphilis. In each case with a prolonged course, remodeling towards cirrhosis occurs. In most patients, the disease is asymptomatic until then and becomes visible only when the changes become permanent. In late-acquired syphilitic hepatitis, histological changes result from the hematogenous invasion of the spirochete into the liver and may become apparent only many years after infection. In the central areas of these foci, necrotic changes are often found, which disintegrate and are replaced by scars associated with increased fibrosis. Inflammatory foci of various sizes usually are located in the peripheral parts of the liver, most commonly in the right lobe, and form typical gummatous lesions (syphilitic gummas). Their location may affect blood flow, leading to Budd-Chiari syndrome, or disturb bile secretion, leading to cholestasis [29].

Diagnosis

Although there are no official criteria for the diagnosis of syphilitic hepatitis, Mullick *et al*. in 2004 proposed the following criteria: 1) elevated liver enzymes indicating liver involvement; 2) positive serological evidence for syphilis; 3) exclusion of alternative causes of liver injury; and 4) improvement in liver enzyme after appropriate antimicrobial therapy [20]. Syphilitic hepatitis can be diagnosed when all four criteria are present.

1. The pattern of liver enzyme abnormalities is typically cholestatic with a marked increase in ALP and

less often GGT. However, hepatocellular or mixed patterns are also observed, with rather mild elevation of transaminases (ALT > AST) and bilirubin level [1].

2. Serologic testing for the diagnosis of syphilis should include both treponemal (TPHA, TPPA, FTA, FTA-ABS, TPI, ELISA) and nontreponemal (USR, VDRL, RPR) tests and either can be used as the initial screening test. The use of only one test is insufficient for diagnosis since serologic testing (especially nontreponemal tests) can be associated with false-positive results [30].

3. Exclusion of other causes of liver injury, e.g.: infection with hepatotropic viruses, autoimmunity, cholelithiasis, Wilson's disease, hemochromatosis.

4. Antibiotic treatment leads to rapid improvement in the majority of cases. According to the available data, significant improvement in transaminases and ALP can be expected as soon as 72 hours after introduction of treatment, usually with normalization up to 16 weeks, although it may be preceded by a transient increase in enzyme activity [1].

As noted above, liver biopsy and imaging tests are not required for diagnosis of syphilitic hepatitis, but may be helpful in establishing the diagnosis.

Gummatous lesions may be seen as multiple, bilobar hypoechoic lesions in ultrasound or as hypoenhancing lesions on CT and MRI mimicking atypical hepatic abscesses or metastatic malignancy [31].

The histopathologic features of syphilitic hepatitis are nonspecific. Usually, mixed lymphoplasmacytic and granulocytic portal or lobular inflammation with variable bile duct injury, cholestasis, hepatocellular necrosis and/or associated noncaseating granulomas are observed. However in some cases vasculotropic and epitheliotropic patterns of inflammation may be seen [4]. Identification of spirochetes in the liver tissue is possible by special Warthin-Starry stain or immunohistochemistry but false negative results are not uncommon [32].

Treatment

Penicillin remains the treatment of choice for patients in all stages of syphilis as *Treponema pallidum* still presents extreme susceptibility to this antibiotic. There are no reports of resistant syphilis. Different regimens are based on the disease stage. Intramuscular administration of benzathine penicillin G 2.4 million IU, in one dose, is recommended in the treatment of early syphilis (primary and secondary). The recommended treatment for late syphilis is a 3-week course of intramuscular benzathine penicillin G at 2.4 million IU once weekly.

Alternative antimicrobial agents include tetracyclines (doxycycline – 100 mg orally twice daily for two or four weeks in early or late syphilis, respectively) and cephalosporins (ceftriaxone – intramuscular or intravenous for 10-14 days, 1 g or 2 g daily in early or late syphilis, respectively). In the case of allergy to beta-lactams doxycycline should be used. Desensitizing to penicillin if allergy testing is positive is indicated in some groups of patients such as pregnant women or patients with ocular, otic, or neurosyphilis [25].

Within the first 24 hours after the first dose of penicillin an idiosyncratic reaction known as the Jarisch-Herxheimer reaction may develop, but it clears up spontaneously without sequelae. It mainly manifests as short-term symptoms such as fever, headache, myalgias and chills [33]. This reaction occurs in approximately 10% to 35% of cases [34].

Patients should be monitored clinically and with serologic testing after the treatment. A fourfold decline in the nontreponemal titer is considered an adequate serologic response. Over time, most patients successfully treated for syphilis experience seroreversion [25].

Disclosure

The authors declare no conflict of interest.

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