Secondary Syphilis With Hepatitis and Nephrotic Syndrome: A Rare Concurrence

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Abstract

Syphilis, a chronic multisystem disease, is caused by a spirochete, Treponema pallidum. Clinical presentation may expand to several stages including primary, secondary and latent syphilis, which may present as early or late syphilis. Nephrotic syndrome and acute hepatitis are well-known complications of secondary syphilis. To the best of our knowledge, secondary syphilis with coexisting renal and hepatic complications has rarely been reported. Here we present a rare case of concurrent nephrotic syndrome and acute hepatitis in a patient with secondary syphilis.

Keywords: Syphilis; Secondary syphilis; Hepatitis; Nephrotic syndrome; Glomerulonephritis

Introduction

Syphilis, a chronic infectious disease, is caused by spirochete Treponema pallidum. Clinical presentation may vary from asymptomatic to systemic disease with multi-organ involvement. The clinical spectrum of syphilis may be primary, secondary, latent, tertiary or congenital based on time and nature of clinical presentation. Secondary syphilis is a systemic disease characterized by maculopapular rash, lymphadenopathy with liver and kidney involvement. Though various forms of hepatitis have been described frequently in literature [1-34], concurrent presentation of both hepatic and renal complications has been rarely described [8, 14, 23, 28, 31, 34]. We present a case of secondary syphilis with features of both hepatitis and nephrotic syndrome.

Case Report

A 51-year-old man presented to emergency room with abdominal pain of 3-week duration and intermittent episodes of bright red blood per rectum for 1 week. He had been in his usual state of health until 3 weeks ago. He described his abdominal pain as dull aching in the epigastric and peri-umbilical regions brought upon by eating. He was also troubled by multiple episodes of non-bilious vomiting over last 3 - 4 days. He was prescribed famotidine by his primary care physician, which did not alleviate his symptoms. He had episodes of rectal bleeding in the past with spontaneous resolution. However, more recently, he has been noticing few streaks of blood mixed with stool especially when he strains to move his bowels. He reported constipation with bowel movement every 3 - 4 days. He denied chest pain, palpitation, shortness of breath, diarrhea, urinary symptoms, fever, loss of appetite or loss of weight.

His medical co-morbidities included diabetes mellitus and osteoarthritis. His current medications included ibuprofen for knee pain, famotidine and metformin. He was using tobacco and alcohol dependent in the past but he had quit more than 15 years ago. He admitted frequent use of recreational drugs like phencyclidine and cannabinoids. He lived by himself and denied any significant family medical history.

On initial evaluation, he was not in distress, afebrile with temperature 98.4° F, pulse 88 beats/min, blood pressure 130/78 mm Hg, respiratory rate 16/min and body mass index (BMI) 27 kg/m². Many copper colored papules and macules were seen on the body including palms and soles of the patient (Fig. 1a, b). He was also noticed to have mild bilateral pitting pedal edema. Rest of his systemic examination including respiratory, cardiac, gastrointestinal and neurological exam was unremarkable.

Laboratory workup during his hospitalization is shown in Table 1. Serological markers of viral hepatitis including hepatitis A, B and C were negative. Autoimmune and metabolic workup for liver disease including anti-nuclear antibody (ANA), smooth muscle antibody (SMA), anti-mitochondrial antibody (AMA), liver kidney microsomal (LKM) antibody, and anti-neutrophil cytoplasmic antibody (ANCA) was tested negative. Metabolic profiles including iron studies, ceruloplasmin and celiac panel were normal. Urinalysis was remarkable with 24-h protein level elevated to 5,915 mg and micro-
albumin to creatinine ratio of 5,250 mg/g. His chest X-ray was unremarkable. Transthoracic echocardiogram showed grade II diastolic dysfunction with normal ejection fraction of 60%. Ultrasound abdomen showed normal liver, spleen, and bilateral kidneys with normal echogenicity and size.

Liver biopsy was performed and histopathology examination (Fig. 2a, b) showed chronic hepatitis with mild activity (grade 2 of 4), portal and peri-portal fibrosis with no fibrous septa (stage 1 of 4). Kidney biopsy showed segmental to global glomerular capillary wall staining for immunoglobulin G (2-3+), complement C3 (2-3+), complement C1 (1+), kappa (2-3+), and lambda (2-3+). Electron microscopy revealed segmental to global subepithelial electron dense deposits and a focus suspicious for a cellular crescent. These findings were diagnostic of an immune complex-mediated glomerulonephritis, most suggestive of membranous glomerulonephritis (MGN). Taken together, diagnosis of secondary syphilis with luetic hepatitis and secondary membranous glomerulonephritis was made. Patient was treated with a single dose of benzathine penicillin G 2.4 million units intramuscularly.

Table 1. Laboratory Parameters

| Parameter     | Value       |
|---------------|-------------|
| Hemoglobin    | 12.7 g/dL   |
| Hematocrit    | 40.8%       |
| White count   | 9,400/μL    |
| Platelet      | 257,000/μL  |
| Sodium        | 125 mEq/L   |
| Potassium     | 4.20 mEq/L  |
| Chloride      | 94 mEq/L    |
| Bicarbonate   | 21 mEq/L    |
| Glucose       | 280 mg/dL   |
| BUN           | 19 mg/dL    |
| Creatinine    | 0.7 mg/dL   |
| Cholesterol   | 263 mg/dL   |
| LDL           | 205 mg/dL   |
| HDL           | 12 mg/dL    |
| Triglyceride  | 231 mg/dL   |
| INR           | 1.0         |
| S. protein    | 7.5 g/dL    |
| S. albumin    | 3.7 g/dL    |
| AST           | 50 Unit/L   |
| ALT           | 91 Unit/L   |
| Alkaline phosphatase | 274 Unit/L |
| Bilirubin (total) | 0.3 mg/dL |
| Bilirubin (direct) | 0.1 mg/dL |
| Lipase        | 43 Unit/L   |
| Amylase       | 31 Unit/L   |
| RPR titer     | 1:1,024     |

Discussion

The term syphilis was first coined by Hieronymus Fracastorius in 1530 but its association with Treponema pallidum was not shown until 1905, when Schaudinn and Hoffman demonstrated them in a smear from syphilitic lesion secretions [35]. In late 1940s after World War II, with the advent of penicillin, cases of syphilis in United States declined tremendously. Since then syphilis cases in United States had several peaks and falls with the all-time lowest in the year 2000 [36]. However, since the year 2000, new syphilis cases in United States have been consistently on a rise mainly among men who have sex with men (MSM) [37].

Mode of transmission is primarily through sexual contact and rarely congenital in which case vertical transmission occurs from an infected mother to the child. Syphilis can affect most organs and tissues of the human body and have varied presentations, hence earning the name “the great imitator”. Syphilis, if left untreated, can progress to different stages, namely, primary, secondary, latent and tertiary. Primary syphilis starts as
a painless indurated ulcer, known as chancre, mostly involving the genitalia. Secondary syphilis has a predominant maculopapular rash, lymphadenopathy with other less common manifestations like meningitis, hepatitis and nephrotic syndrome. Latent syphilis as the name suggests is an asymptomatic stage and the infected individual is diagnosed based on the positive serology. Tertiary syphilis can be cardiovascular in the form of aortitis, or neurosyphilis that may present as meningitis, vasculitis, paresis, tabes dorsalis and gumma formation [35].

Simultaneous involvement of liver and kidney in secondary syphilis is very rare [8, 14, 23, 28, 31, 34]. Albuminuria is the most common renal manifestation in secondary syphilis. Clinically, it has a wide range of presentation from transient asymptomatic albuminuria to symptomatic nephritic or nephrotic syndrome. Pathogenesis involves direct damage by spirochetes as well as autoantibodies and immune complexes. Membranous nephropathy is the most common etiology for nephrotic syndrome. Membranous nephropathy is the most common renal manifestation in secondary syphilis. Other findings in syphilitic renal disease include mesangial proliferative glomerulonephritis, post-infectious endocapillary proliferative glomerulonephritis, rapidly progressive glomerulonephritis with crescents, minimal change disease, renal gumma and amyloid renal disease [38].

Literature on syphilitic hepatitis, also known as luetic hepatitis, has been very sparse. Most of the patients are asymptomatic but in very rare instances present with right upper quadrant abdominal pain [4]. It is now recognized that in syphilitic hepatitis, there is an elevation of transaminases with or without cholestasis. Liver biopsy shows non-specific perportal inflammation and necrosis with or without spirochetes. Liver injury occurs as a result of direct damage by spirochetes as well as via autoimmune antibodies and immune complex mediated mechanisms [39, 40].

Other gastrointestinal manifestations of syphilis are gastropathy and proctitis which may also coexist with hepatitis [6]. Gastropathy can appear like peptic ulcer disease but often has poor response to the usual treatments of peptic ulcer disease. Histologically shallow superficial ulcerations, dense mucosal monocytic and plasma cell infiltration, edema, characteristic proliferative endarteritis and panphlebitis are the most frequent findings. Syphilitic proctitis involves anal and rectal lesions that occur from anal intercourse, especially among homosexual men. Clinically, it may mimic hemorrhoids but proctoscopy shows an irregular, indurated lesion with heaped-up margins and multiple small ulcerations. Biopsy specimen shows a mononuclear cell infiltrate, vasculitis and in some cases spirochetes [6].

Diagnostic methods have evolved over several years, but attempts to culture the organism have been unsuccessful. Dark field microscopy remains the quickest and most useful method to identify the organism. However, it has high false negative rates. Serological testing is the most frequently used method of testing for secondary, latent and tertiary syphilis. Serological tests are divided into two categories - non-treponemal and treponemal tests. Non-treponemal tests include Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) test that detect antibodies against cardiolipin. Treponemal tests, fluorescent treponemal antibody absorption (FTA-ABS) and micro-hemagglutination assay for Treponema pallidum (MHA-TP) antibodies have higher sensitivity and specificity as compared to non-treponemal tests [41].

Penicillin G is the drug of choice due to its sustained therapeutic troughs of penicillin G and high susceptibility of Treponema pallidum. Single intramuscular injection of 2.4 million units of benzathine penicillin G is the preferred treatment for primary, secondary and early latent syphilis. Ceftriaxone has been used as an alternative by some researchers. Other drugs used to treat Treponema pallidum, especially in patients allergic to penicillin, are tetracycline or erythromycin. Treatment for neurosyphilis requires 10 - 14 days of therapy with aqueous crystalline penicillin G or procaine penicillin with probenecid [42]. Jarisch-Herxheimer reaction is an immunologically mediated reaction in response to syphilis treatment. It comprises constitutional symptoms like fever, myalgia, headache and worsening of cutaneous lesions [43]. There were also reports confirming resolution of hepatitis and renal complications with penicillin G therapy.

Syphilis is a sexually transmitted systemic disease with a broad spectrum of manifestations involving various organs at different stages of the disease. Liver and renal involvements in secondary syphilis are well-known complications. However, coexistence of liver and renal disease in secondary syphilis is very rare. Our case chronicles this rare co-existence and stresses on various presentations of syphilis as we see resurgence in the incidence of syphilis and enable timely recognition with appropriate management.
Conflicts of Interest

Authors have no conflicts of interest to disclose.

Author Contributions

Jasbir Makker and Bharat Bajantri wrote the manuscript. Suresh Nayudu reviewed the manuscript.

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