Hepatitis in Scarlet Fever

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The frequency of hepatitis in children with scarlet fever is unknown but appears to be rare. We present a boy who developed subicteric hepatitis several days after onset of scarlet fever. Physicians treating patients with scarlet fever and group A beta-hemolytic Streptococcus infections should be aware of this association.

The term scarlet fever first came into general use in the nineteenth century although historically the disease can be traced back to 429 bc, when an epidemic of what appears to have been scarlet fever was documented in Athens. Scarlet fever is caused by an erythrogenic toxin-producing group A beta-hemolytic Streptococcus and is characterized clinically by a typical fine red rash, swollen red tongue (strawberry tongue) and desquamation. Septic or severe scarlet fever may be complicated by arthritis, jaundice and hydrops of the gallbladder [1,2]. However, hepatitis with or without jaundice as an early manifestation of scarlet fever has rarely been reported, and most of these reports are not recent. We describe a patient recently admitted to our hospital with scarlet fever associated with hepatitis.

Patient Description

A 9 year old boy presented with a 4 day fever of 40°C, a typical scarlatiniform rash (including the abdomen and genitalia), lymphadenopathy and sore throat. A throat swab culture was performed and antibiotic treatment with amoxicillin was started.

Four days later he was still febrile, suffering from abdominal pain, nausea, vomiting, and dark-colored urine. GABHS was cultured from the throat swab. Physical examination was normal without liver or spleen enlargement or jaundice.

Laboratory tests revealed elevated levels of serum transaminases, aspartate aminotransferase 40 U/L, glutamate-pyruvate transaminase 90 U/L, gamma-glutamyl transferase 70 U/L, with total bilirubin 1.5 mg/dl and direct bilirubin 0.5 mg/dl. Lactate dehydrogenase and alkaline phosphatase levels were within normal range. Prothrombin time and albumin were normal. Full blood count was also normal. C-reactive protein was high, 5 mg/dl. Erythrocyte sedimentation rate was 50 mmHg. Serum assays for immunoglobulins M and G antibodies against Epstein-Barr virus, cytomegalovirus and hepatitis A, B and C were all negative. Antistreptolysin O test, which was 200 IU/ml on admission, rose to 800 IU/ml 2 weeks later.

Ultrasound examination of the liver and gallbladder was unremarkable. On the 10th day desquamation of the fingertips began. After 20 days of rehydration and bed rest, the patient fully recovered and liver function test were normal.

Comment

Since the first report on hepatitis associated with scarlet fever in 1931, only a few cases have been published. In 1952, Sato [2] obtained liver biopsies from two children with scarlet fever without jaundice and found cytoplasmic swelling and granularity along with portal infiltrations by mononuclear cells. In 1976, Kocak [2] noted jaundice and elevated liver functions in two girls in the early phase of scarlet fever. Needle biopsy study of the liver in one of the girls revealed polymorphonuclear granulocytes infiltrating the portal area and degenerative changes in the hepatocytes. Similar findings were found in liver biopsies performed in adults with streptococcal infections and laboratory evidence of hepatitis [2].

In an autopsy series of 59 cases of scarlet fever jaundice was found in 4 (2). Postmortem cultures of blood and lungs yielded beta-hemolytic streptococci, whereas cultures of liver tissue did not.

Girisch and Heninger [3] reported on two boys with scarlet fever and hepatitis without jaundice. In their review of the literature they noted that the reported cases of hepatitis in association with scarlet fever frequently occurred several days after onset of the skin rash. Most of the patients presented with full-blown jaundice, but some were subicteric. The authors suggested that hepatitis may often be overlooked in patients with scarlet fever and that the hepatotoxic effect might be caused by streptococcal pyrogenic exotoxins [3].

Group A streptococcal pyrogenic exotoxins are believed to be central mediators of the systemic inflammation seen in severe streptococcal infections. These “superantigens” do not require processing by antigen-presenting cells and can interact with a variety of class II major histocompatibility complex molecules. The superantigen-MHC complex, in turn, interacts with T cell receptors, eliciting cytokine responses and activating a large proportion of the immune cells [4]. Endotoxins can activate hepatic macrophages and sinusoidal endothelial cells, leading to an excess secretion of cytokines and intrasinusoidal coagulation and thereby injuring hepatocytes [5]. It is possible that HLA polymorphism influences the susceptibility to the superantigens. It has been proven that patients with severe and non-severe man-
Ifestations have a propensity to produce different levels of cytokine responses to the same superantigens, which may explain the inter-individual diversity of clinical manifestations observed in streptococcal infections [4].

Our patient was treated with amoxicillin before the hepatitis developed. There are several reports of an association between amoxicillin treatment and toxic hepatitis, but most involve a combination of amoxicillin and clavulanic acid. In addition, the clinical and pathologic findings were predominantly cholestatic. This complication is also fortunately rare [3]. Our patient did not have a cholestatic disorder, and he was treated with amoxicillin only.

In conclusion, we present a boy who developed subicteric hepatitis several days after onset of scarlet fever. We assume that the hepatitis was a complication of the GABHS infection. The negative tests for other infectious causes of hepatitis and the marked improvement while under antibiotic treatment support this assumption. Physicians treating patients with scarlet fever should be aware of this association.

References

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**Geopolitical Intrusion on Editorial Decisions**

World Association of Medical Editors (WAME) Statement, posted 23 March 2003

Decisions to edit and publish manuscripts submitted to biomedical journals should be based on characteristics of the manuscripts themselves and how they relate to the journal’s purposes and readers. Among these characteristics are importance of the topic, originality, scientific strength, clarity and completeness of written expression, and potential interest to readers. Editors should also take into account whether studies are ethical and whether their publication might cause harm to readers or to the public interest.

Editorial decisions should not be affected by the origins of the manuscript, including the nationality, ethnicity, political beliefs, race, or religion of the authors. Decisions to edit and publish should not be determined by the policies of the governments or other agencies outside of the journal itself.

Editors should defend this principle, as they do other principles of sound editorial practice, and enlist their colleagues’ support in this effort if necessary.

The WAME Policy Statement on geopolitical intrusion on editorial decisions is now available on the WAME site at http://wame.org/wamesmtm.htm

The Israel Medical Association, publisher of IMAJ (Israel Association Medical Journal) and Harefuah (Hebrew), endorses the above statement.

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**Capsule**

**Lysosomes in health and disease**

Waste materials in cells are transported to the lysosome for destruction, but lysosomes have roles to play in cells beyond being dustbins. Stinchcombe et al. review the role of a specialized class of lysosomes important in a variety of cell types that defy definition as a final resting place for defunct material. In certain cell types, especially in cells of the immune systems, lysosomes can do double-duty as secretory organelles.

Several genetic disorders of the immune system involve defects in the functions of secretory lysosomes. Similarities in the membrane-traffic pathways involved in secretory lysosomes and melanocytes mean that, in some rare genetic disorders, immune dysfunction and albinism are linked.

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