

Scarlet fever associated with hepatitis in pediatrics. A case report

Hepatitis asociada a escarlatina en pediatría. Reporte de caso

Arvind V. Panchoo^a, Miguel Saps^b, Edgardo D. Rivera Rivera^b

^aDepartment of Pediatrics, Jackson Memorial Hospital

^bDivision of Pediatric Gastroenterology, Hepatology and Nutrition, University of Miami, Miller School of Medicine

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Abstract

Introduction: Scarlet fever is a common illness in pediatrics caused by group A beta-hemolytic streptococcus (GABHS), which usually occurs after an episode of pharyngitis, and has an overall excellent prognosis. Hepatitis secondary to scarlet fever is a rare complication described in adults and even less frequently in children. Our objective was to describe a case of hepatitis secondary to scarlet fever in a pediatric patient. **Clinical Case:** A 12-year-old male with scarlet fever presented with a 4-day history of jaundice, dark urine, and decreased appetite. Laboratory tests revealed elevated liver enzymes and total and direct bilirubin levels, and negative studies for hepatitis A, B and C, Epstein Barr virus, parvovirus B19, adenovirus, cytomegalovirus, human herpes virus-6, and herpes simplex virus 1 and 2. Abdominal ultrasound examination was normal. **Discussion:** The pathogenesis of scarlet fever associated hepatitis remains unclear. Streptococcal pyrogenic exotoxin mediated cellular injury via cytokine production has been proposed as a possible mechanism of hepatotoxicity in GABHS infections. **Conclusion:** Hepatitis secondary to scarlet fever remains a rare but benign entity, with complete recovery expected over weeks to months.

Keywords:

Scarlet Fever; hepatitis; group A beta-hemolytic streptococcus; pediatrics

Resumen

Introducción: La escarlatina es una enfermedad común en Pediatría, causada por Estreptococo beta hemolítico grupo A (SBHGA), la cual generalmente se presenta después de un episodio de faringitis, y con excelente pronóstico general. La hepatitis secundaria a escarlatina es una complicación, descrita muy rara vez en niños. Nuestro objetivo fue reportar la ocurrencia de hepatitis secundaria a escarlatina en un paciente pediátrico. **Caso Clínico:** Varón de 12 años cursando escarlatina, quien se presentó con una historia de 4 días de ictericia, coluria y disminución del apetito. Los exámenes de laboratorio revelaron elevación de las transaminasas y de los niveles de bilirrubina total y directa, y estudios virales negativos para Hepatitis A, B y C, Virus de Epstein Barr, Parvovirus B19, Citomegalovirus, Virus Herpes 6 y Herpes simplex 1 y 2. Ecografía abdominal fue normal. **Discusión:** La hepatitis es una complicación inhabitual de la escarlatina, cuya patogénesis aún no está clara. La producción de citoquinas a través del daño celular mediado por la exotoxina pirógena estreptocócica, se ha propuesto como un posible mecanismo de hepatotoxicidad en infecciones por SBHGA. **Conclusión:** La hepatitis asociada a escarlatina continúa siendo una entidad rara, pero de curso benigno, con recuperación plena en semanas a meses.

Palabras clave:

Escarlatina, hepatitis; Estreptococo grupo A beta-hemolítico; pediatría

Correspondencia:
Arvind V. Panchoo
arvind.panchoo@jhsmiami.org

Introduction

Scarlet Fever is a common pediatric illness caused by group A beta hemolytic *Streptococcus* (GABHS), usually following an episode of pharyngitis^{1,2}. Typically, it is characterized by fever, a red colored tongue and fine erythematous rash followed by desquamation^{1,3}. Rheumatic fever, glomerulonephritis, septic arthritis, osteomyelitis, pneumonia and otitis media are some of the well-documented complications of GABHS infection^{1,2}. Nevertheless, with appropriate antibiotic treatment scarlet fever carries an overall excellent prognosis. Hepatitis secondary to scarlet fever is a rare complication described in adults and even less frequently in children². Though the association between scarlet fever and hepatitis was first reported in 1931, the pathogenesis still remains largely unknown, and there exist only few pediatric cases in the literature highlighting the course, prognosis and eventual outcomes of these patients¹⁻⁶. Herein, we report a pediatric case of scarlet fever associated with hepatitis, the first to the best of our knowledge in over fifty years in North America. The objective of this article is to raise awareness among pediatricians regarding possible hepatic involvement with scarlet fever.

Clinical case

A 12 year old male with recently diagnosed scarlet fever presented to our institution with a four day history of jaundice, dark urine and decreased appetite. His illness began nine days prior to admission with fever and sore throat. On the third day he developed an erythematous, papular rash of the face, trunk and extremities. He was taken to an urgent care center where a rapid antigen test (throat swab) for group A *Streptococcus* was found to be positive. Subsequently, the

patient was diagnosed with scarlet fever and started on a five day course of amoxicillin.

In our emergency department, his vital signs were all stable and normal for age. Physical examination revealed bilateral scleral icterus, fine, erythematous, papular rash over the face, trunk and extremities without abdominal tenderness, hepatomegaly or splenomegaly. Initial laboratory evaluation was significant for hemoglobin of 11.8 g/dl [Reference Range 11-16g/dl], elevated white blood cells of 20,300/ml [Reference Range 4,500-13,000/ml] with a neutrophil predominance, normal electrolyte and renal function profile, elevated anti-streptolysine O (ASO) titer of 209 IU/ml [Reference Range < 200 IU/ml], elevated liver enzymes and elevated total and direct bilirubin levels (Table 1). Urinalysis was positive for bilirubinuria without proteinuria, hematuria or pyuria. Ultrasound examination of the liver, gallbladder and biliary system was unremarkable, with the spleen demonstrating normal echogenicity and size.

At that point the Pediatric Gastroenterology service was consulted and further investigations were performed. These included antibody serology tests for hepatitis viruses A, B and C, hepatitis B surface antigen, antinuclear antibody, DNA polymerase chain reaction (PCR) for Epstein Barr virus, parvovirus B19, adenovirus, cytomegalovirus, human herpes virus 6, herpes simplex virus 1 and herpes simplex virus 2. All of these resulted negative. Serum ceroplasmin and C3 and C4 complement levels were also sought and were found to be in the normal range.

The patient was provided with symptomatic care and by day eleven of illness his rash began to fade, and desquamation of the palms and soles was observed. He was discharged with good oral tolerance following a stable hospital course. At outpatient follow up three weeks later, he was asymptomatic with resolution of icterus and down trending liver enzymes (Table 1).

Table 1. Laboratory Parameters with Reference Ranges in Parenthesizes

Laboratory parameter	Day 1 of admission	Day 2 of admission	Day 3 of admission	Day 4 of admission	Day 5 of admission	Outpatient Visit
AST (15-46 units/L)	151	189	177	249	267	70
ALT (21-72 units/L)	256	273	273	297	293	79
A LP (114-501 units/L)	361	415	471	510	514	498
GGTP (3-18 units/L)	649		862	934	867	
Total Bilirubin (0.2-1.3 mg/dl)	5.8	5.7	5.6	4.4	4.0	1.0
Direct Bilirubin (0-0.4 mg/dl)	5.0	4.8	4.6	3.7	3.3	

AST= aspartate aminotransferase; ALT= alanine aminotransferase; ALP= alkaline phosphatase; GGTP= gamma-glutamyl transpeptidase.

Discussion

The incidence of hepatitis with scarlet fever in pediatrics is not known, but by all accounts seems to be rare. Contributing to this uncertainty are published cases of hepatitis in scarlet fever without jaundice, leading some authors to believe that hepatitis may simply be missed or overlooked in scarlet fever without icterus^{3,5}.

Girisch and Heinger on review of the literature noted that hepatitis appears to closely follow the development of the characteristic rash⁵. As in our case, the patient developed a fine erythematous, papular facial rash on day three of illness and then experienced onset of jaundice and dark urine on the sixth day, with elevations of liver enzymes discovered soon after.

Though first described by MacMahon and Mallory in 1931, the pathogenesis of liver involvement in scarlet fever remains unclear⁴. In an autopsy series of fifty-nine cases of scarlet fever, post-mortem cultures of lung tissue and blood yielded growth of GABHS but those from liver tissue did not; arguing against direct bacterial hepatic injury¹. However, streptococcal pyrogenic exotoxin mediated cellular injury has been proposed as a possible mechanism of hepatotoxicity in GABHS infections. It is believed that such exotoxins have the ability to interact with both the major histocompatibility complex molecules of antigen presenting cells and T-cell receptors, thereby acting as 'super antigens', with the end result of stimulating T cells to produce cytokines capable of inciting liver injury⁷.

It has been demonstrated that individuals produce varying degrees of cytokine responses to the same streptococcal super antigen. In that study, the investigators noted that patients with a propensity to produce higher levels of cytokines experienced more significant systemic manifestations than those who produce lower levels of cytokines in response to the same streptococcal super antigen⁸. Indeed, in preparing this report we came across two cases of hepatitis in scarlet fever associated with gallbladder hydrops; one even describing splenomegaly and ascites^{3,9}. All of this is to say, that there may exist, a spectrum of scarlet fever disease presentation, possibly attributed to host factors affecting the level of lymphokine production in response to GABHS infection, with scarlet fever associated hepatitis being on the more severe end of the range.

Patients presenting with a clinical picture of cholestatic hepatitis in the setting of scarlet fever raises a number of etiological considerations. Leptospirosis for instance shares many similar features seen in our patient, namely; jaundice, fever, neutrophilic leukocytosis and even various skin exanthemas has been observed in this disease process¹⁰. The absence of sig-

nificant abdominal tenderness, hepatomegaly, splenomegaly, myalgia, headache, renal involvement and history of exposure to infected animals (dogs, rodents) makes this condition less likely. Bradycardia and high remittent fever have been described in association with leptospirosis¹⁰, none of which occurred during our patient's disease course.

Many of the clinical features observed in this case can be attributed to Kawasaki disease and typhoid fever. Our patient described a four day history of intermittent fever and never exhibited mucous membrane changes, bilateral conjunctival injection or cervical lymphadenopathy, hence his presentation did not meet the diagnostic criteria for complete Kawasaki disease¹¹. Kawasaki disease can be associated with mild to moderate elevations of serum transaminases and hyperbilirubinemia but without objective evidence of at least five days of fever and other supplemental laboratory criteria such as pyruia and thrombocytosis (platelet count $> 500 \times 10^3/\text{microL}$), incomplete Kawasaki disease remains very unlikely¹². Typhoid fever was essentially ruled out given the lack of characteristic salmon-colored spots on trunk and abdomen, bradycardia or travel to areas where this illness is endemic³.

Since our patient presented with cholestatic hepatitis and received amoxicillin, some readers may question whether this may have been secondary to amoxicillin use. Hepatitis is a very rare occurrence with amoxicillin treatment, having a six fold higher incidence when a combination of amoxicillin and clavunate is used. Also, such reports describe older patients with longer durations of antibiotic use¹³. Our patient was prescribed a five day course of only amoxicillin.

Scarlet fever is diagnosed largely on clinical manifestations but in equivocal cases pharyngeal culture and ASO titers are followed¹⁴. ASO titers begin to rise after 1 week of illness and peaks in three to five weeks³. Given a history of fever, sore throat, characteristic rash with desquamation, a positive rapid antigen test for group A Streptococcus and elevated ASO titers the authors feel confident that this patient's cholestatic hepatitis is associated with an initial presentation of scarlet fever.

At outpatient follow up, liver enzymes were noted to have decreased significantly, though still mildly elevated from normal. Unfortunately the patient has defaulted from outpatient visits but has expressed to clinical staff the absence of jaundice, dark urine, pale stools and abdominal pain in a telephone interview four months post hospital discharge.

To the best of our knowledge, this report presents the first case of scarlet fever associated with hepatitis in over fifty years in North America. The last, described

an 18 year old female admitted to a University Hospital in Maryland in 1962. Scarlet fever was diagnosed based on typical clinical symptoms and positive pharyngeal culture, with hepatitis noted on liver biopsy¹⁰. Since then other cases have been sporadically identified in various nationalities^{1-6,9,15,16}.

Conclusion

Many healthcare providers, including general pediatricians may not be aware of this entity, potentially leading to thorough investigation and a more prolonged hospital course that can significantly increase the cost of health care. With this case we aim to raise awareness among pediatricians regarding possible hepatic involvement with scarlet fever and underline that such patients generally follow a benign disease course with complete recovery expected over several weeks to months.

Responsabilidades Éticas

Protección de personas y animales: Los autores declaran que los procedimientos seguidos se conformaron a las normas éticas del comité de experimentación humana responsable y de acuerdo con la Asociación Médica Mundial y la Declaración de Helsinki.

Confidencialidad de los datos: Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado: Los autores han obtenido el consentimiento informado de los pacientes y/o sujetos referidos en el artículo. Este documento obra en poder del autor de correspondencia.

Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

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