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RUBELLA INFECTION FOLLOWING ORTHOTOPIC LIVER TRANSPLANTATION

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Rubella is usually a mild disease of childhood characterized by rash, lymphadenopathy, low grade fever and leukopenia. The major morbidity associated with rubella is the development of congenital infection when disease occurs in susceptible pregnant women[1]. The prevalence and outcome of rubella in susceptible solid organ transplant recipients are unknown. This case report describes a 13-year-old liver transplant recipient who underwent evaluation for fever and adenopathy and was found to have rubella.

CASE REPORT

A 13-year-old native Argentinian boy who underwent orthotopic liver transplantation (OLT) for Crigler-Najjar Syndrome one year previously presented with a one week history of painful cervical lymphadenopathy and low grade fever. His post-transplant course had been unremarkable. At the time of admission he denied any history of rhinorrhea, cough, conjunctivitis, sore throat, nausea, vomiting, diarrhea or rash. His father reported that the patient had a recent exposure to rubella in his school and that he had never been immunized against this agent. His medications consisted of florinef, trimethoprim-sulfamethoxazole and the experimental immunosuppressant FK 506 at an oral dose of 2.5 mg twice daily.

On admission, the patient was afebrile and well appearing. Physical examination revealed multiple right anterior and posterior cervical lymph nodes. The largest node was a right jugulodigastric node that measured 0.5 x 1.5 cm. A left axillary

node was present that measured 1.0 x 0.5 cm. The tonsils were normal in size; there was neither erythema or exudate. There was no hepatosplenomegaly. The remainder of his physical examination was unremarkable.

The white blood cell count was 4.8 x 10^3 cells/mm^3 with 43% neutrophils, 42% lymphocytes, 6% monocytes, 3% eosinophils, 1% basophils and 5% atypical lymphocytes; the platelet count was 121,000/mm^3. Serum electrolytes, BUN and creatinine were within normal limits. The gamma-glutamyl transferase was slightly elevated at 89 IU/L (upper limit normal = 44 IU/L); the remainder of the patient's liver injury tests were normal. CT scans of the chest and abdomen were normal; no adenopathy was noted.

The right jugulodigastric lymph node was excised. Histologic examination of the lymph node showed reactive changes consisting of paracortial expansion without immunoblastic changes. Viral cytopathic effects were not seen.

Titers for Epstein-Barr virus (EBV) obtained both prior to and at the time of this admission were consistent with past infection without evidence of reactivation or reinfection (VCA-IgG > 50 with negative titers against VCA-IgM, Early Antigen and Nuclear Antigen). A pre-transplant screen for antibodies against rubella was negative. Repeat serologies showed IgM antibody > 50 EU/ml and a positive titer for IgG.

Bacterial and viral cultures of blood and urine were negative. Interference assays for rubella using Echovirus 11 were performed on viral cultures obtained from the lymph node,

throat, urine and blood. The assays from both the throat and lymph node were positive suggesting the presence of rubella virus in these cultures.

Initial management of this patient consisted of decreasing his dose of FK 506 to 2.0 mg twice daily. The patient was discharged and followed up as an outpatient when results of his serologic tests and lymph node biopsies were known. His lymphadenopathy resolved within one month and he continues to do well.

DISCUSSION

The widespread use of live rubella vaccine in the United States has resulted in a markedly decreased incidence of rubella[2]. However, such vaccination is not routinely practiced in many other regions of the world, including Argentina, and in these areas clinical rubella remains endemic. The increasing incidence of acquired immunodeficiency syndrome in children in areas were rubella remains endemic raises concern about the potential development of severe disease from this usually mild infection. The symptoms experienced by our patient were modest; suspicion for rubella was raised by the history of exposure in a susceptible individual. Although rubella is classically associated with rash, it commonly occurs in 25% - 50% of patients without the presence of an exanthem[3-5]. Lymphadenopathy is a major manifestation of disease, and the low-grade fever and mild leukopenia present in our patient are typical.

Serologic testing is the primary mode of diagnosing rubella.

The presence of IgG and IgM antibody in a patient not recently vaccinated substantiates a recent rubella infection. The diagnosis of rubella is confirmed by viral culture of nasal or throat specimens. The presence of rubella infection in cell cultures is detected utilizing inoculated African Green Monkey Kidney cell cultures that are superinfected with echovirus 11 and observed for the development of a characteristic cytopathic effect[6]. The inhibition of the enterovirus-mediated cytopathic effect demonstrates the presence of rubella virus. Two specimens from our patient demonstrated this interference effect confirming the diagnosis of rubella.

Low-grade fever and lymphadenopathy in a liver transplant recipient appropriately initiates an evaluation for the presence of EBV-associated post-transplant lymphoproliferative disease (PTLD), as well as other viruses or infectious processes which may cause lymphadenopathy. PTLD was suspected in this patient based upon the timing and clinical presentation and the relatively high incidence of PTLD in pediatric OLT recipients (4.7%)[7]. EBV and the resultant PTLD is the most important viral infection to occur more than six months after pediatric liver transplant. Presentation in OLT patients on cyclosporine typically occurs in the first six months to one year after transplant, however cases as late as six years post transplant have been reported[8]. Clinical findings range from exudative tonsillitis, adenopathy and fever (as seen in classical mononucleosis) to solitary or multiple nodules subsequently

diagnosed as lymphoma. The morbidity and mortality associated with this process and the relatively high-rate of response to withdrawal of immunosuppression mandates confirmation of the diagnosis. Review of our experience suggests that outcome is improved with earlier recognition, reinforcing the need to react promptly in patients with a typical clinical presentation.

The diagnosis of EBV-associated PTLD was abandoned in our patient because imaging procedures showed no abnormalities and neither serologic nor histopathologic examinations were supportive. If the patient was proven to have PTLD he would typically have been treated in the hospital with a minimum of two weeks of intravenous acyclovir and withdrawal of immunosuppression until the onset of rejection. Instead, the patient was discharged after a four day hospitalization on a minimally decreased dose of FK 506.

The presence of lymphadenopathy in the immunocompromised, post-transplant patient is compatible with a variety of infectious processes. The most frequent and important of these is EBV-associated PTLD. Other infections, including rubella, cat scratch disease (Apalsch A, et al. Ped Inf Dis J. in press)[9], atypical mycobacteria and other causes of regional or diffuse adenopathy may mimic PTLD in presentation. An awareness of the differential diagnosis of lymphadenopathy is necessary, especially in the pediatric population where non EBV-associated conditions may occur. Careful evaluation allow differentiation between these processes and guides appropriate management of these patients.

REFERENCES

1. Feigen RD and Cherry JD: Textbook of Pediatric Infectious Disease. WB Sauders Co. 1992.

2. Bart KJ, Orenstein WA, and Hinman AR: The virtual elimination of rubella and mumps from the United States and the use of combined measles, mumps and rubella vaccines (MMR) to eliminate measles. Developments in Biological Standardization 1986; 65:45-52.

3. Green RH, Balsamo MR, Giles JP, et al.: Studies on the natural history and prevention of rubella. Am J Dis Child 1965; 110:348.

4. Sever JL, Brody JA, Schiff GM, et al.: Rubella epidemic on St. Paul Island in the Pribilofs JAMA 1963; 191:624-626.

5. Horstmann DM, Riordan JT, Ohtawara M, et al.: A natural epidemic of rubella in a closed population. Virological and epidemiological observations. Arch Ges Virusforsch 1965; 16:483-487.

6. Krugman S, Katz SL, Gershon AA, and Wilfert CM: Infectious Disease of Children. Mosby Yearbook, 1992.

7. Reyes J, Tzakis A, Green M, et al.: Post transplant lymphoproliferative disorders occurring under primary FK 506 immunosuppression. Transplant Proc December 1991; 23(6):3044-3046.

8. Matalach JJ, et al.: Orthotopic liver transplantation, Epstein-Barr virus, cyclosporine, and lymphoproliferative disease: a growing concern. Journal of Pediatrics May 1991; 118:667-675.

9. Apalsch AM, Nour B, Jaffe R: Systemic Cat Scratch Disease in a pediatric patient and review of the literature. Pediatric Infectious Dis J (in press).