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CLINICAL VIGNETTE

Recurrent Episodes of Unexplained Fever, Lymphadenopathy, and Rash

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A 20-year-old female with no significant PMH presents with high fever to 104, new onset groin lymphadenopathy, and rash over her buttocks for two days. She was in her usual state of health until she developed sudden onset of pain in her groin area and noticed that she had painful lymphadenopathy. Over a 24-hour period, she developed generalized weakness, myalgias in the upper legs, lightheadedness, and fever up to 104 degrees. She also developed a rash over her bilateral buttocks, which is non-pruritic, non-painful, and not spreading. She had intermittent headaches with her fevers but denies any neck stiffness, photo- or phonophobia. She denies any diarrhea, abdominal or pelvic pain, shortness of breath, chest pain, urinary symptoms, vaginal discharge, changes in vision, sore throat, cough, runny nose, or upper respiratory symptoms.

She reports having similar symptoms of fever, groin pain with inguinal lymphadenopathy, and rash four years prior. She was admitted to the hospital at that time, but all infectious and rheumatologic work-up was negative, including a negative lumbar puncture. However, Streptolysin O Antibody (ASO) was moderately elevated to 609 IU/mL, but she did not have any symptoms of streptococcal pharyngitis. She was treated with ceftriaxone and amoxicillin and symptoms resolved after four days.

She reports the prior episode also included severe joint pains, and a more diffuse rash, which also included her chest. The rash took months to resolve, changed colors during resolution to blue and purple, and finally faded and resolved. She has been otherwise healthy during the interim four year period.

She denies eating any new or different foods and denies any sick contacts. She denies any recent personal illness, and her last travel was to Israel for 10 days about 3 months prior. She has no pets at home nor do her friends. She drinks alcohol at most a few drinks a week with friends, none recently. She never smoked cigarettes and denies drug use. She is sexually active with her boyfriend of 3 months; they are in a monogamous relationship and use condoms consistently for birth control. She denies any history of sexually transmitted infections. She had a pelvic exam 2 years ago when she was tested for sexually transmitted infections, including HIV, and all tests were negative. Last menstrual period was 2 weeks prior. She uses tampons during her menstrual cycle but hasn't used one in over 2 weeks since her last cycle ended. She received all her childhood vaccines. She does not get a yearly flu vaccine.

Her physical exam was significant for fevers up to as high as 40.3 degrees Celsius, heart rate up to 125, and systolic blood pressure as low as 100. She had diffuse tender moderately sized cervical lymphadenopathy and no supraclavicular or axillary lymph nodes. She had large, firm, confluent, tender lymphadenopathy along the right groin without overlying erythema or ulcerations, left groin with four isolated small tender lymph nodes. There were no vaginal ulcers or lesions. She had shaved pubic hair without any folliculitis. Her posterior buttocks had diffuse erythematous confluent blanching rash, warm, and non-tender extending distally on R>L to her lower thigh and proximally up to the mid back on the R side.

Extensive blood and urine testing was negative for bacterial, viral, or ricketsial infections. Rheumatologic serologies and chest x-ray were normal. CT scan of the abdomen and pelvis showed prominent inguinal and left periaortic lymph nodes but was otherwise unremarkable. Right inguinal lymph node biopsy revealed a reactive lymph node with paracortical hyperplasia and sinus histiocytosis. Flow cytometry demonstrated no monotypic B cell population and no discrete pan T-cell aberrancies. There was no evidence of lymphoproliferative disorder, confirmed by immunohistochemistry.

Based on test results, the patient was diagnosed with sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). All symptoms including lymphadenopathy, fever, and rash resolved within 10 days without intervention.

Discussion

Sinus histiocytosis with massive lymphadenopathy (SHML) is a rare, benign disorder of immune regulation or response to a presumed infectious agent with resulting proliferation of sinusoidal histiocytes within lymph nodes. The exact etiologic agent has not been identified. The lymphocyte response is a benign reactive process rather than neoplastic.

Clinical Features

The majority patients present within the first two decades of life. The male to female ratio is 1.4 to 1. 62% of patients are less than the age of 10 at presentation; however, the average age is reported as 19 years.[1]

The most frequent clinical manifestation of SHML is bilateral, painless cervical lymphadenopathy often referred to as "bull neck." Other nodal sites are involved as well including mediastinal, retroperitoneal, and inguinal sites.

Extranodal disease has been reported in 30% of cases with predilection within the head and neck and cutaneous involvement. Other reported sites include the abdominal viscera, testicles, meninges, and cranium. Nasal involvement presents with symptoms of nasal obstruction and rhinorrhea. Orbital involvement typically manifests as proptosis. When the trachea is affected, stridor or dyspnea may occur. Cutaneous involvement has presented in some cases as subcutaneous nodules or rash that usually precedes the lymphadenopathy.

In addition to massive lymphadenopathy, other associated symptoms often include low-grade fever, leukocytosis with left shift and neutrophilia, and elevated erythrocyte sedimentation rate. Sixty percent of patients have a normocytic anemia. Eighty-five percent have polyclonal hypergammaglobulinemia.[2]

The disease course is often indolent and self-limited. One third of patients will have residual asymptomatic adenopathy. The natural course and outcome are variable, usually indolent, and characterized by remissions and exacerbations over many months to years. The lymphadenopahty usually resolves spontaneously. One third of patients have disease for greater than five years. Fatal outcomes have occurred in less than 7% of cases, usually in patients with concurrent immune deficiencies.

Diagnosis

Diagnosis is based on lymph node biopsy and characteristic histological features. The gross morphology includes large lobulated masses with the presence of fibrous septae between lymph nodes. The microscopic features are distinguished by engorgement of dilated nodal sinuses with large distinctive histiocytes with ample pale cytoplasm. Characteristic for this disease is a process known as emperipolesis, which is the presence of an intact lymphocyte cell within the cytoplasm of a histiocyte cell.[2]

Treatment

Although the literature contains no specific treatment protocol, various modalities have been tried in severe or progressive cases. The approach in these cases is similar to treatment of low-grade lymphomas including chemotherapy and radiation. Surgical treatment has been used when nodal or extranodal disease causes tracheal obstruction, spinal cord impingement, or intracranial involvement.

REFERENCES

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