Infectious Mononucleosis Presenting as Raynaud's Phenomenon

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Infectious mononucleosis is a common illness caused by the Epstein-Barr virus. While it is frequently seen in young adults with its typical presentation (ie, pharyngitis, fever, lymphadenopathy, lymphocytosis with an elevated percentage of atypical lymphocytes, and serologic evidence of heterophile antibodies), the clinical manifestations of infectious mononucleosis are myriad and include jaundice, myocarditis, splenic rupture, autoimmune hemolytic anemia, and neurologic complications such as encephalitis, optic neuritis, Guillain-Barré syndrome, and Bell's palsy.[1,2] This article describes a patient with infectious mononucleosis who presented with Raynaud's phenomenon, a previously unreported association, and discusses the implication of this case report.

CASE REPORT

A 21-year-old man was seen in the Family Practice Center at Thomas Jefferson University with a 5-day history of cold-induced "blue" fingers, toes, ears, and nose. The patient also reported a 1-month history of headaches, a 2-week history of generalized fatigue, poor appetite, and neck myalgias, and a 1-week history of sore throat. He had attributed most of his symptoms to the significant stress he had been experiencing. Within the preceding 3 months, he had been married, his new wife had been diagnosed as having multiple sclerosis, his new father-in-law had died from recently discovered lung cancer, and he had temporarily discontinued his full-time college education to work in his recently deceased father-in-law's business. His medications had included only aspirin for his recent headaches. He had used two cans of smokeless tobacco per week for the past 6 years; however, he had discontinued this habit 2 months prior to his present symptoms.

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On initial examination, the patient's fingers were noted to be cyanotic, as were his ears and nose. After warming up to the inside office temperature, however, his cyanosis disappeared, and he developed increasing erythema, especially in his hands and ears, with reddish streaks over his face. The remainder of his physical examination was within normal limits. After all of his symptoms resolved in the office, the patient's hand was immersed in ice water, whereupon he exhibited the classic changes of Raynaud's phenomenon: pallor, cyanosis, and rubor. Initial laboratory tests included a hemoglobin of 135 g/L (13.5 g/dL), hematocrit of 0.38 (38%), and white blood cell count of 9.3 $\times$ 10^9/L (9300 mm^{-3}), with 0.48 (48%) lymphocytes and 0.12 (12%) atypical lymphocytes. His erythrocyte sedimentation rate was markedly elevated at 72 mm/h. The alkaline phosphatase (4.4 μkat, 262 U/L), lactic dehydrogenase (LDH) (7.55 μkat, 453 U/L) and aspartate aminotransferase (AST) (88 U/L) were all elevated. The antinuclear antibody was 1:160 with a speckled pattern, and the serum immunoelectrophoresis was normal, as were the serum creatinine and total bilirubin. A rapid slide test for heterophile antibody infectious mononucleosis was positive.

The patient was seen 2 days later without further symptoms. Physical examination at that time also revealed an erythematous pharynx with exudate and a 1-cm left axillary lymph node, which was nontender and freely moveable. A urinalysis at that time was within normal limits, and a throat culture was performed, which grew normal flora. Over the next month, episodes of cold-precipitated Raynaud's phenomenon became less frequent and then stopped. The patient's headaches and sore throat had resolved, although he still complained of some anorexia and fatigue. One month after his initial presentation, immersion of the patient's hands in ice water showed changes that were less marked than in previous visits. Repeat laboratory tests at this time showed the white blood cell count to be 8.0 $\times$ 10^9/L (8000 mm^{-3}) with 0.29 (29%) lymphocytes and 0.01 (1%) atypical lymphocytes. The erythrocyte sedimentation rate had returned to normal (3 mm/h), as had the AST, LDH, and alkaline phosphatase. The gamma-glutamyl transpeptidase (GGT) was slightly elevated (0.97

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μkat/L, 58 U/L).

The patient was last seen 2½ months after his initial presentation. He had had no further episodes of Raynaud's phenomenon, and he had complete resolution of his fatigue and anorexia. Immersion of his hands in ice water at this time produced no abnormal changes. His white blood cell count, erythrocyte sedimentation rate, GGT, and alkaline phosphatase had all returned to normal.

DISCUSSION

This patient presented with the classic triphasic response of Raynaud's phenomenon in reaction to cold temperatures.[3] He also had the typical clinical picture, hematologic changes, and serologic response of infectious mononucleosis, ie, a young adult with sore throat, malaise, fatigue, headache, pharyngitis, abnormal liver function tests, a relative and absolute lymphocytosis with an elevated percentage of atypical lymphocytes, and a positive heterophile antibody test.[2,3]

Previous reports have not described the association of infectious mononucleosis and Raynaud's phenomenon. Mononucleosis has, however, been associated with a large number of antibodies (in addition to the commonly measured heterophile antibody), including cold agglutinins, as well as with cryoglobulinemia.[2,4,5] Both of these hematologic abnormalities, although not specifically measured in this patient, have previously been associated with Raynaud's phenomenon in other patients.[3,6,7] In addition, a prior case report describing a 5-year-old child with infectious mononucleosis presenting as cold-induced acrocyanosis secondary to cold agglutinins may well represent a phenomenon similar to that described in the present case.[8]

Although rapid heterophile tests have a sensitivity and specificity of greater than 95%, they are not diagnostic of infectious mononucleosis, and occasionally false-positive results have been reported in leukemia, lymphoma, rubella, malaria, hepatitis, and other diseases.[9,10] In the presence of the typical clinical and laboratory manifestations of infectious mononucleosis, however, determination of Epstein-Barr antibody titers have not been deemed necessary and were not obtained in this patient.[10,11] Although the combination of Raynaud's phenomenon and a low-titer antinuclear antibody test may suggest the possibility of other diseases, such as systemic lupus erythematosus, antinuclear antibodies have also been found in infectious mononucleosis,[12] and the patient reported in this case lacked any additional diagnostic criteria for lupus. In addition, the complete resolution of the patient's symptoms and laboratory results, compatible with the clinical course of infectious mononucleosis, makes a second diagnosis unlikely.

The case report presented in this paper suggests that infectious mononucleosis needs to be included in the list of diseases causing Raynaud's phenomenon. Additional cases need to be identified, and appropriate serologic data obtained. While cold agglutinins or cryoglobulinemia have been suggested as a possible mechanism whereby Raynaud's phenomenon developed secondary to infectious mononucleosis, it is unclear why this association has not previously been recognized, especially since infectious mononucleosis is a common problem and since cold agglutinins and cryoglobulins are frequently present. Also unclear is the role stress plays, although stress has been implicated in both infectious mononucleosis and Raynaud's phenomenon, and was clearly present in this case. Finally, while the treatment of Raynaud's phenomenon depends on its primary cause, Raynaud's disease remains an illness without a known etiology, pathophysiology, or adequate therapy.[3,6] Future studies of the immunologic abnormalities of patients with infectious mononucleosis and Raynaud's phenomenon may help to further define the mechanism of peripheral vasospasm and shed further light onto the treatment of Raynaud's disease.

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