Paraneoplastic stiff-person syndrome, heterotopic soft tissue ossification and gonarthritis in a HLA B27-positive woman preceding the diagnosis of Hodgkin's lymphoma

Paraneoplastic neurologic syndromes associated with Hodgkin's lymphoma include the stiff-person syndrome. A case of stiff-person syndrome is reported who first presented with muscular hyperactivity and acute respiratory failure followed by heterotopic soft tissue ossification and acute seronegative gonarthitis. Initial improvement of a tetanus-like clinical picture was achieved with benzodiazepam given by continuous infusion for analgo-sedation to mechanically ventilate the patient followed by baclofen after successful weaning. The patient was HLA B27 positive and on conventional testing no autoantibodies were detected including anti-glutamic acid decarboxylase antibodies (anti-GAD). Months later in the absence of signs of stiff-person syndrome, mediastinal lymphadenopathy and pleural effusions developed which were diagnosed as classical Hodgkin's lymphoma that was successfully treated with polychemotherapy. No relaps of paraneoplastic neurologic syndromes was seen after two years of lymphoma remission. The case illustrates that stiff-person syndrome may precede the clinical appearance of symptomatic Hodgkin's lymphoma.

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Several rare paraneoplastic neurologic syndromes have been described in patients with Hodgkin's lymphoma. These include paraneoplastic cerebellar degeneration, chorea, neuromyotonia, limbic encephalitis, subacute sensory neuronopathy, subacute lower motor neuronopathy, and the stiff-person syndrome (SPS).[1-8] Paraneoplastic neurologic syndromes do not correlate with the severity of Hodgkin's lymphoma and may develop while the patient is in remission.[9]

SPS is an uncommon disorder characterized by progressive muscle stiffness, rigidity, and spasm involving the axial muscles.[10] The disorder often occurres in conjunction with a variety of autoimmune diseases. Antibodies were found to target GABAergic (gamma amino butyric acid) neurons and their nerve terminals. The dominant antigen recognized by these antibodies is the GABA-synthesizing enzyme, glutamic acid decarboxylase (GAD). Based upon the presence or absence of specific antibodies as well as other diseases, patients with SPS have been subdivided into the autoimmune, paraneoplastic and idiopathic variants.

Case presentation

A 55 year-old woman was in good health before presenting with a three-day history of back pain and stiffness of her trunk causing difficulty in bending forward and turning over while lying down. She then became febrile and developed asymmetrical stiffness of the legs and difficulty walking. On examination her initial mental status, speech, and cranial nerves were normal. She had exaggerated lumbar lordosis. Neurological examination showed increased tone of the flexors and extensors of the knee and ankles. She had flexor plantar responses. Power and coordination were normal, deep tendon reflexes were brisk. Sensory examination was normal. A chest radiograph and computerized tomography (CT) of the brain were normal.

Because tetanus-like muscle activity and painful spasms progressed to include dysphagia and respiratory insufficiency, orotracheal intubation was performed and mechanical ventilation started. With benzodiazepine-including analgo-sedation which was administered because of mechanical ventilation, her muscle activity was significantly reduced. However, pulmonary function increasingly deteriorated over the next days and ventilator-associated pneumonia was diagnosed. After three weeks of mechanical ventilation weaning from mechanical ventilation was initiated after successful treatment of pneumonia and septic shock with antibiotics and hemodynamic management. As benzodiazepine administration was reduced, increased muscle activity returned. Lumbar puncture, cerebral angio-CT and magnetic resonance tomography (MRI) were all normal. Antibody testing was negative including anti-GM(1) ganglioside and anti-GAD. Symptomatic therapy with baclofen was begun and the patient was admitted for physical rehabilitation as muscle weakness that has developed after weaning from analgo-sedation persisted which was then attributed to critical illness polyneuropathy. Baclofen has been stopped after eight weeks of prescription. Muscular hyperactivity had disappeared.

After discharge from the intensive care unit, physical therapy was performed for four months but was only moderately effective in ameliorating persistent muscle weakness. Then sudden swelling and pain of the left knee developed. Except a positive test result for HLA B27, no evidence of associated genitourinary or intestinal infections was obtained. Urine and stool cultures for arthritis-causing organisms were negative as was testing for antimicrobial antibodies including HIV and autoimmune disease markers. MRI of the knee confirmed heterotopic ossification also noted around the hip in a plain radiograph that had already been taken before symptoms of arthritis were seen. Soft tissue sarcoma was excluded. On physical examination, tonsils, base of the tongue, nasopharynx and standard lymph node sites including cervical, supraclavicular, axillary, inguinal, and femoral were normal. The patient was not febrile and night sweats were absent. Work-up included CT scans of chest, abdomen and pelvis. Whereas spleen, abdominal and pelvic lymph nodes were normal, subcarinal mediastinal adenopathy was observed with no parenchymal abnormalities, pericardial or chest wall involvement. Laboratory parameters including white blood cell differential counts and liver functions tests were normal. Erythrocyte sedimentation rate was 44 mm/hour. Tissue biopsy from the mediastinum of a total of 13 lymph nodes failed to identify malignancy. Histopathology of a synovial biopsy from the left knee excluded lymphomatous infiltration of the synovium. Indomethacin 150 mg/day taken in three divided doses was sufficiently effective in controlling pain and signs of inflammation and the patient was discharged to outpatient care after a period of three weeks.

After another 8 months, 14 months after initial presentation, the patient again presented with dyspnea on exertion (New York Heart Association Stage II). A chest radiograph indicated pleural effusions that were lymphocytic and chylous on diagnostic pleurocentesis suggesting mediastinal inflammation. Blood tests showed mild leukocytosis of 11.4 G/L with 93% neutrophils and 7% lymphocytes, lactate dehydrogenase was 248 U/L (upper limit of normal, 223 U/L) and C-reactive protein at 1.97 mg/dL (upper limit of normal, 1.00 mg/dL). Liver, bone and renal function, including serum alkaline phosphatase,

aspartate aminotransferase, alanine aminotransferase, and serum calcium were normal. Erythrocyte sedimentation rate this time was 8 mm/hour. Repeat cerebral, chest, abdominal and pelvic CT scans revealed extensive mediastinal lymphadenopathy in anterior, paraaortic, paratracheal, subcarinal and left-sided hilar location. Radiological evidence suggested parenchymal involvement as other likely causes, particularly infection, were absent. CT results could not rule out lymphoma with splenic involvement but CT alterations in spleen were not confirmed by abdominal ultrasonography. No evidence of bone marrow infiltration by malignant cells was obtained. CT-guided biopsy of mediastinal lymph nodes revealed classical nodular sclerosis Hodgkin lymphoma. Clinical staging indicated advanced mediastinal disease with mediastinal and hilar adenopathy and lung parenchymal involvement II(e). Pleural effusion confirmed bulky mediastinal disease. Polychemotherapy was performed with ABVD doxorubicin, bleomycin, vinblastine and dacarbazine for a total of x 8 cycles. The patient went in complete remission and follow-up procedures after initial treatment every three months for a total of 3 times are without evidence of relapse. Muscle weakness without evidence of hyperactivity persisted despite successful treatment of Hodgkin's lymphoma.

Discussion

The majority of patients with Hodgkin's lymphoma present with overt disease, most often as an asymptomatic enlarged lymph node or a mass on chest x-ray. A significant proportion of patients with Hodgkin's lymphoma develop systemic symptoms prior to the discovery of lymphadenopathy. However, the presenting symptoms and signs may be relatively nonspecific. Several rare paraneoplastic neurologic syndromes have been described in patients with Hodgkin's lymphoma. These include paraneoplastic cerebellar degeneration, chorea, neuromyotonia, limbic encephalitis, subacute sensory neuronopathy, subacute lower motor neuronopathy, and the SPS.

Over the past 25 years, approximately 150 cases of SPS have been reported in the medical literature. Women appear to be affected more often than men.[10] Episodic muscle spasm precipitated by sudden movement, noise, or emotional upset is a sensitive and specific feature of SPS. Spasms usually begin in the axial muscles and may spread to the extremities. Other than an abnormal gait and hyperreflexia, the motor and sensory nerve examinations are usually normal. Electromyographic studies reveal continuous motor-unit activity which is typically decreased or abolished by intravenous diazepam, and local or general anesthesia.[11] Benzodiazepines are generally considered the optimal initial therapy for patients with SPS. There are no studies to guide the choice of initial drug. The association of SPS with malignancy requires that the clinician be vigilant for these diagnoses.

Signs and symptoms in the current patient resembles to large extent typical presentation of SPS. Initial differential diagnosis included tetanus that was excluded and the clinical response to benzodiazepam followed by baclofen was seen as in SPS.

Associations of SPS with type I diabetes, thymoma, myasthenia gravis, thyroiditis, adrenal insufficiency, vitiligo, and pernicious anemia have been reported.[11-13] Two cases of Borrelia burgdorferi myelitis (Lyme disease) presenting with features of stiff person syndrom have also been described.[14-15] None of the autoimmune associations could be confirmed in our patient even though the complication of acute gonarthritis was suggestive. However, not autoantibody against any of the organs or tissues could be detected nor was antibody testing positive for anti-GAD.

The paraneoplastic variant consists of patients with associated neoplasms and circulating non-organ-specific autoantibodies, but without anti-GAD and anti-islet cell antibodies.

HLA B27 carriers are predisposed to inflammatory and autoimmune diseases. In patients with haematological diseases including Hodgkin lymphoma, HLA B27 carriers are also more frequent, and the association of arthritis with haematological diseases in HLA B27 carriers has been noted.[16] This suggests that HLA-B27 carriers may have an increased risk not only of ankylosing spondylitis but also of haematologic malignancies.

In the present case of a HLA B27 positive woman, Hodgkin's lymphoma was associated with sero-negative left-sided gonarthritis and myositis ossificans, which is a heterotopic ossification of skeletal muscles which is commonly seen after trauma. It has rarely been seen as a complication of tetanus[17] but its association with SPS has not been reported. Heterotopic ossification is also a recognized complication in patients with head injury, burns, paraplegia, or direct trauma to muscle tissue, and is considered rare in hemiplegia following stroke.[18] Patients at moderate risk of heterotopic ossification include those with ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis, Paget's disease, or unilateral hypertrophic osteoarthritis.[19] The HLA B27 allele does not occur more commonly in the genotype of patients with fibrodysplasia ossificans progressiva than in the general population, and the pathogenesis of heterotopic bone in fibrodysplasia ossificans progressiva differs from that of ankylosing spondylitis and other HLA B27 positive disorders.[20]

If the two complications, gonarthtitis and heterotopic ossification, are related to prolonged immobilization during critical care treatment and persistent muscular weakness of critical illness polyneuropathy or to paraneoplastic autoimmune phenomena of Hodgkin's lymphoma remains unknown. Inflammation around the enthesis is relatively specific for spondyloarthropathy including reactive arthritis and is strongly associated with HLA B27[21] as was also the case in our patient's gonarthritis. The enthesis is the site of insertion of ligaments, tendons, joint capsule, or fascia to bone that it is susceptible to antigen deposition.

Spontaneous regression has been observed in Hodgkin's lymphoma and it is well known that its lymphadenopathy may vary during its spontaneous clinical course.[22,23] Failure to identify Hodgkin's lymphadenopathy on mediastinal biopsies taken at the time of presentation of acute gonarthritis some weeks after initial SPS symptoms may well reflect waxing and waning of the malignant disease in its initial phase.

As a significant proportion of patients with Hodgkin's lymphoma develop systemic symptoms prior to the discovery of lymphadenopathy, and as the presenting symptoms and signs may be relatively non-specific, paraneoplastic presentation may have to be considered even in the absence of confirming histopathology. Early and frequent follow-up examination and observation of the patient's clinical course may be required if paraneoplastic origin of presenting symptomptoms cannot be excluded. In conclusion, the case illustrates that stiff-person syndrome may precede the clinical appearance of symptomatic Hodgkin's lymphoma.

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