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 gonarthritis. Initial improvement of a tetanus-like clinical picture was achieved with benzodiazepine 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 relapses 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.

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). Paraneoplastic neurologic syndromes do not correlate with the severity of Hodgkin’s lymphoma and may develop while the patient is in remission. SPS is an uncommon disorder characterized by progressive muscle stiffness, rigidity, and spasms involving the axial muscles. The disorder often occurs 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 (MRT) 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, subarcinal 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,
None of the autoimmune associations of SPS are specific. Associations of SPS with type I diabetes, thymoma, paraneoplastic cerebellar degeneration, choroid plexus papilloma, hyperparathyroidism, and paraneoplastic antibodies are described in patients with Hodgkin's lymphoma. These associations remain unknown. Inflammation around the enthesis is well known to be associated with reactive arthritis and is strongly associated with HLA B27. Inflammation around the enthesis is also associated with ankylosing spondylitis. HLA B27 is overrepresented in the general population, but its association with SPS remains unknown.

Electromyographic studies reveal continuous motor-unit activity which is typically decreased or abolished by intravenous diazepam, and reveal prolonged fibrillations and positive sharp waves. The clinical response to benzodiazepine followed by baclofen is usually 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. Over the past 25 years, approximately 150 cases of SPS have been reported in the medical literature. Women present with pain and stiffness of the proximal muscles, and men present with pain and stiffness of the distal muscles. The majority of patients with SPS present with pain and stiffness of the proximal muscles. HLA B27 carriers are predisposed to inflammatory and paraneoplastic diseases including Hodgkin's lymphoma. HLA B27 carriers also have an increased risk of spondyloarthropathy and perivascular inflammation.

The majority of patients with SPS present with overactivity, most often as an asymptomatic subjective complaint. However, the diagnosis of SPS depends on the presence of hyperreflexia, the motor and sensory nerve examination of patients with SPS. Spasms usually begin in the axial muscles and may be precipitated by sudden movement, noise, or emotional stress. The SPS syndrome may be caused by local or general anesthesia. The association of SPS with malignancy requires that the clinician be vigilant for these diagnoses. The present case of a HLA B27 positive woman with SPS and Hodgkin's lymphoma was associated with sero-negative paraneoplastic antibodies. The paraneoplastic variant consists of patients with Hodgkin's lymphoma and it is well known that its association with SPS remains unknown. The role of a rare event in the development of SPS is well known. The association of SPS with malignancy requires that the clinician be vigilant for these diagnoses. Over the past 25 years, approximately 150 cases of SPS have been reported in the medical literature. Women present with pain and stiffness of the proximal muscles, and men present with pain and stiffness of the distal muscles. The majority of patients with SPS present with pain and stiffness of the proximal muscles. HLA B27 carriers are predisposed to inflammatory and paraneoplastic diseases including Hodgkin's lymphoma. HLA B27 carriers also have an increased risk of spondyloarthropathy and perivascular inflammation.
References