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CLINICAL COMMUNICATION

Parsonage–Turner syndrome during the treatment of HIV/HHV8-related multicentric Castleman disease

Síndrome de Parsonage-Turner durante el tratamiento de la enfermedad de Castleman multicéntrica asociada a VIH y herpes humano 8

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Introduction

The Parsonage–Turner syndrome (PTS) is a rare entity characterized by acute pain and atrophy of the shoulder girdle muscles due to an acute inflammatory neuropathy of the brachial plexus. It may be bilateral, with associated sensory deficit and/or phrenic nerve involvement.[1,2] The aetiology of this syndrome is unknown, but various infections and immunological and genetic factors have been involved. The association of PTS with human immunodeficiency virus (HIV) infection has been previously documented elsewhere.[3–6]

Castleman disease (CD) is an uncommon non-clonal lymphoproliferative disorder, which may be classified as unicentric CD (UCD) or multicentric CD (MCD). MCD is associated with a significant systemic inflammatory response with elevation of various inflammatory mediators, and is characterized by multiple enlarged lymph nodes. MCD may occur in association with other lymphoproliferative disorders, Kaposi's sarcoma or autoimmune disorders.

A patient with MCD associated with HIV and human herpes virus 8 infections who developed PTS during the course of treatment with rituximab is described.

Case report

A 46-year-old man was diagnosed with HIV infection in 2008 and had been receiving anti-retroviral treatment with emtricitabine, tenofovir and nevirapine for the last 3 years. He had an undetectable viral load and 504 CD4 cells/μl. The patient presented with a 3-week history of fever, asthenia, sweats and weight loss of 4–5 kg. On examination he had cervical and axillary lymphadenopathy, hepatomegaly and splenomegaly (palpable 3–4 cm below the left costal margin). Blood tests revealed elevation of inflammatory markers (C-reactive protein: 144 mg/l; erythrocyte sedimentation rate: 71 mm in the first hour and fibrinogen: 697 mg/dl), anaemia (haemoglobin 10 g/dl), polyclonal hypergammaglobulinemia (IgG and IgA) and a small IgG Kappa monoclonal band. Epstein–Barr and cytomegalovirus IgG antibodies were positive and IgMs antibodies were negative; HHV8 IgG antibody was positive and IgM antibodies was negative (ELISA). Thoracic and abdominal computerized

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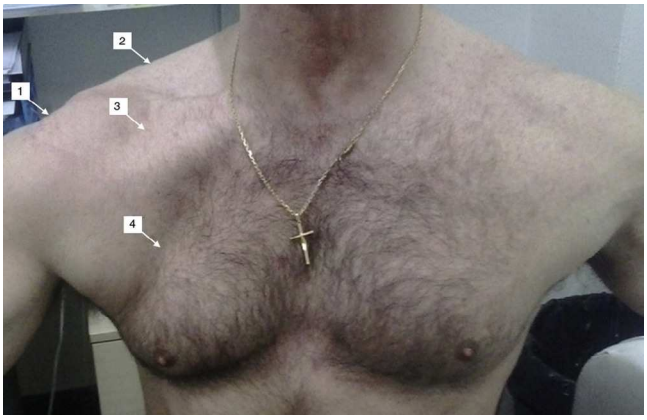

Figure 1 Anterior view: shoulder asymmetry may be observed with atrophy of the right deltoid, trapezius, and pectoralis major (clavicular and sternocostal portions) muscles (arrows 1–4, respectively).

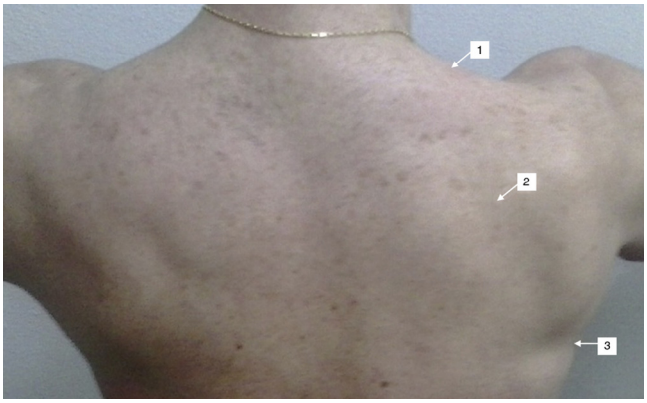

Figure 2 Trapezius, infraspinatus and teres major muscular atrophy (arrows 1–3, respectively).

tomography (CT) scans confirmed peripheral lymphadenopathy and revealed mediastinal and retroperitoneal lymphadenopathy and homogeneous splenomegaly. All enlarged lymph nodes showed enhancement following intravenous contrast administration, suggesting an increase in vascularization. A cervical lymph node biopsy revealed changes consistent with the plasma cell variant of CD [(CD20 (+) and bcl-2 (−) lymphocytes and polyclonal kappa (+) and lambda (+) plasma cells].

The patient was treated with rituximab (4 weekly doses of 375 mg/m^2) with clinical improvement and stabilization of blood parameters. During the third and fourth week of treatment, the patient referred weakness of the right shoulder, with no associated pain or paraesthesia. On examination, there was weakness and atrophy of the right shoulder girdle muscles and a diminished biceps and triceps reflex (Figs. 1 and 2). A chest X-ray showed left hemidiaphragm elevation, which was not present in previous X-rays (Fig. 3A and B). Electromyography confirmed the presence of a demyelinating motor neuropathy of the superior branches of the right brachial plexus. A follow-up CT scan performed 8 weeks after treatment with rituximab revealed no lymphadenopathy or splenomegaly, although left hemidiaphragm elevation persisted. The patient followed a rehabilitation programme with progressive improvement, although mild atrophy and motor weakness remained after 6 months.

Discussion

The patient had a chronic HIV infection and maintained a stable immuno-virological status when he developed MCD. During treatment with rituximab and with apparent complete remission of MCD, he presented symptoms suggestive of PTS. The patient did not experience the characteristic localized pain which may be found in up to 97% cases of PTS and which has also been observed previously in a patient with HIV infection.[4] However, the patient in the current report did have other typical features of PTS such as muscular atrophy, consistent findings in the neurophysiological studies performed and simultaneous contralateral phrenic nerve involvement. Previous descriptions of PTS in HIV patients have occurred in association with primary HIV infection,[3,5] whereas in the current report PTS developed during the chronic phase of HIV infection and occurred concurrently with MCD and rituximab treatment. Bellagamba

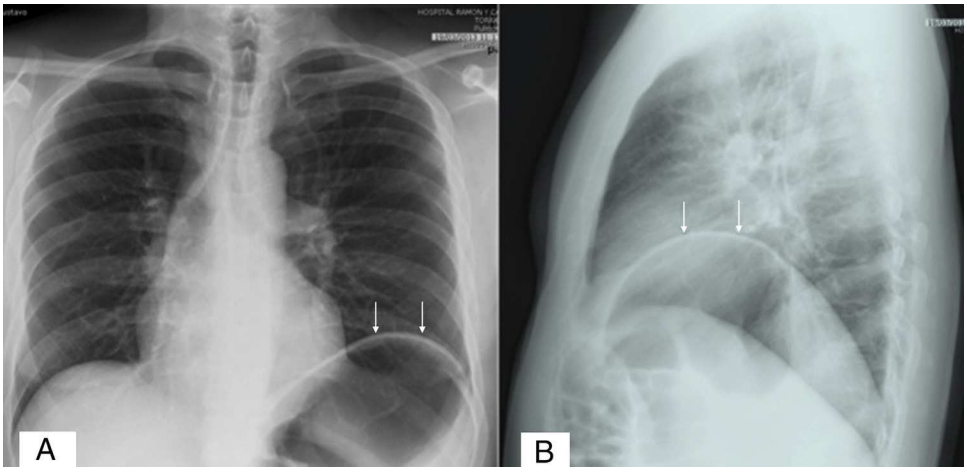

Figure 3 Posteroanterior (A) and lateral (B) chest X-ray showing left hemidiaphragm elevation (arrows).

et al.[6] reported a case of PTS due to hypersensitivity to abacavir in a patient with chronic HIV infection.

PTS or brachial plexus polyneuropathy was first described in 1948.[7] The incidence of this syndrome is low (1.63–3 cases per 100,000 persons per year), although this entity may be under-diagnosed. In several cases, an infection has been documented between 2 and 14 days before the symptoms initiated and these infections were mainly viral or bacterial in origin. PTS may also occur in association with systemic autoimmune diseases, following vaccination or trauma, peripartum, following surgery or after strenuous physical exercise.[1,2] Examination of the cerebrospinal fluid (CSF) may reveal albumin-cytologic dissociation and oligoclonal bands.

MRI studies have shown hyperintense T2 signals suggestive of neurogenic oedema in cases of acute/subacute denervation of the shoulder girdle muscles.[8] However, there are no specific MRI findings, which may aid in the diagnosis of PTS. MRI findings may vary depending on when the scan is performed and may be normal if performed early on in the course of the disease. MRI is mainly used to exclude other diseases that may present with similar clinical manifestations.

In the current case, the HIV+/HHV8+ MCD and the administration of rituximab may have contributed to the development of PTS. The association of HIV and MCD has previously been established, and co-infection with HHV8 occurs in the majority of cases. An acute or recent HHV8 infection is not considered necessary for the development of MCD, and virus is generally detected in tissues if in situ hybridization, PCR or immunohistochemistry techniques for detection of nuclear antigen are performed. MCD in HIV-positive patients usually runs a more aggressive course. No cases of PTS in HIV-associated MCD have previously been described[9]; nevertheless, Dossier et al. reported a single case of bilateral brachial paralysis in a patient with MCD and HHV8 infection who was HIV negative.[10] However, these authors found CSF lymphocytosis and possible tissue infiltration on MRI, suggesting that involvement of the brachial plexus with lymphoma may have occurred. In the current case, PTS developed after initiating rituximab treatment for MCD with a favourable clinical response. Several published cases highlight the possible adverse effects of new biological treatments, such as various forms of demyelinating peripheral neuropathies (including optic neuritis, polyradiculopathy or chronic inflammatory demyelinating polyneuropathy).[11] Cases of isolated brachial plexus involvement in patients treated with biological therapies, and specifically with rituximab, have not been reported in the literature to date. A case of lumbar plexus neuropathy due to varicella zoster virus, dorsal myelitis and idiopathic brachial plexus neuropathy similar to PTS in a patient treated with infliximab has been described.[12]

HIV and HHV8 associated MCD variants are currently considered separate entities. Production of HHV8-mediated inflammatory cytokines, such as IL-6, may hypothetically lead to the systemic symptoms in MCD and might have a role in the development of autoimmune manifestations, such as PTS-like neuropathy. However, PTS has not previously been described in association with MCD.[9,10]

The possible relevance of the monclonal IgG kappa band in the development of PTS should be considered. This finding may have suggested an underlying monoclonal gammopathy of unknown significance (MGUS) with associated neuropathy or a POEMS syndrome (*Polyneuropathy*, *Organomegaly*, *Endocrinopathy*, *Monoclonal band and Skin changes*) associated with MCD. PTS has not previously been associated with MGUS and in the case of the POEMS syndrome, the neuropathy generally involves the lower limbs, runs a chronic and progressive course and the monoclonal band is of the lambda type in 95% of the cases, making these possibilities unlikely.

The majority of patients with PTS improve spontaneously after a few weeks. Pain usually precedes weakness and usually disappears as atrophy develops, but may persist and become refractory to conventional analgesia. Early steroid use may reduce pain and rehabilitation should be recommended to prevent disuse atrophy.[1,2]

PTS may be an autoimmune neurological manifestation of HIV/HHV8 associated MCD. In this case, administration of rituximab may have contributed to the development of PTS.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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