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Sjögren-like pluriglandular exocrine insufficiency after drug-induced toxic epidermal necrolysis

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Summary: We present the case of a patient that progressively developed xerophthalmia, xerostomia, cutaneous xerosis and exocrine pancreatic insufficiency 3 months after metamizole-induced toxic epidermal necrolysis. Though the association of Sjögren's syndrome and exocrine pancreatic impairment is well established, the Sjögren-like syndrome after drug-induced toxic epidermal necrolysis in association with such a wide exocrine glandular insufficiency has not been previously described, to our knowledge.

Introduction

Toxic epidermal necrolysis (TEN) is the most severe skin disease attributed to a drug reaction.[1] Because of the association between toxic epidermal necrolysis and graft-versus-host disease[2,3] and the occurrence of sicca syndrome as sequela in patients with toxic epidermal necrolysis,[4] it is generally assumed that toxic epidermal necrolysis has an immunologically mediated origin.[5] We present the case of a patient that progressively developed xerophthalmia, xerostomia, cutaneous xerosis and exocrine pancreatic insufficiency 3 months after metamizole-induced toxic epidermal necrolysis. Though the association of Sjögren's syndrome and exocrine pancreatic impairment is well established,[6] the Sjögren-like syndrome after drug-induced toxic epidermal necrolysis in association with such a wide exocrine glandular insufficiency has not been previously described, to our knowledge.

Case report

A 55 year old woman was admitted to hospital because of weight loss. In her personal history, cervicoarthrosis was notable, which was treated with multiple non-steroidal anti-inflammatory drugs, although the patient was unable to specify which ones. Five months before admission and 30–35 hours after the intramuscular administration of 2 g of metamizole (Nolotil®, Europharma) the patient began to notice progressively confluent erythematous lesions, with no target lesions, that developed in 24 hours to a generalized tender cutaneous erythema that affected 100% of the body surface area, with a temperature of 39–40°C, prostration, sore throat and conjunctivitis. This was immediately followed by the formation of flaccid bullae that resulted in the peeling of sheets of skin leaving painful denuded areas. The patient presented eroded areas of the lips, mouth, conjunctivae, anal and genital mucosae. Progressive reepithelization of skin and mucous membranes took place in 3–4 weeks. The patient had never before experienced any reaction to hydantoins, non-steroidal anti-inflammatory drugs or penicillin. She did not know if she had been previously treated with noramidopyrine but had not received any medication for the previous 3 months. She referred no viral infection or cold symptoms.

Since presenting this picture the patient had been afebrile, but presented asthenia and progressive anorexia, xerostomy with difficulty swallowing, a 'sandy' sensation in her eyes, cutaneous xerosis, progressive loss of weight (20% of her body weight in 5 months) and daily and nightly diarrhoea during the 4 months before admission.

On admission the patient was generally unwell. She had dry and peeling skin on arms and legs, and a dry oral mucosa. The liver edge was 2 cm from the costal border. Laboratory studies revealed the following positive data: gamma glutamyl transpeptidase 133 U/l (normal 50 to 7), aspartate aminotransferase 45 U/l (normal 40 to 4), alanine aminotransferase 63 U/l (normal 40 to 4), lactic dehydrogenase 524 U/l (normal 460 to 230) and alkaline phosphatase 398 U/l (normal 280 to 98). The tests for antinuclear antibodies, antimitochondrial antibodies, anti-smooth muscle antibodies and anti-Ro antibodies were negative. Total fat in stools was 44.4 g/24 h (normal $<$ 5 g/24 h) and the

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neutral fat was increased (12.56 g), the D-xylose absorption test (25 g-oral dose) revealed a 5-h urinary excretion of 4.85 g (normal > 4.0 g) and the pancreolauryl test a 5% fluorescein excretion (severe pancreatic exocrine insufficiency) (normal > 25%). Serological tests for viral hepatitis B were negative. The upper gastrointestinal series, radiological study of the large intestine and endoscopic retrograde cholangiopancreatography were normal, without evidence of chronic pancreatitis. The ultrasonographic studies of the abdomen revealed a slight hepatomegaly without other pathological findings. Ophthalmological examination indicated the existence of a keratoconjunctivitis sicca (Schirmer's test: 3/4 [right eye/left eye] mm/5 min) (normal ⩾ 10 mm wetting per 5 min); and 7 points on the van Bijsterveld score (abnormal if ⩾ 4 points on a 0–9 points scale). The unstimulated whole sialometry revealed a salivary flow rate of 0.5 ml/15 min (abnormal if ⩽ 1.5 ml/15 min). The histopathological findings of the hepatic tissue were reported as consistent with a nonspecific reactive hepatitis. The lip biopsy revealed marked fibrosis, atrophy and inflammatory infiltration in seven minor salivary glands. Histopathological studies of multiple samples of small bowel mucosa obtained via peroral biopsy were normal.

Discussion

Drug-induced TEN has been characterized by acute onset, severe morbidity and high mortality.[7] The pathogenesis of the disease is not known. Non-steroidal anti-inflammatory drugs are the most common cause of TEN in many series. Specially frequent are the phenylbutazone and oxicam derivatives. Even though aminopyrine or noramidopyrine have been reported as culprit drugs in a few cases of drug-induced TEN, these drugs are more often cited for the early manifestations of toxic epidermal necrolysis.[8] In the last 10 years, only 5 cases of metamizole-induced TEN have been reported,[8–10] and a single case of Sjögren-like syndrome after metamizole-induced TEN has been described by Roujeau *et al.*[4]

Persistent ocular lesions are the most disabling sequelae of TEN.[11] Ocular dryness is rarely observed during the acute phase of TEN, more often symptoms develop within a few weeks. A high percentage of patients with dry eyes also had reduced salivary flow. Sicca syndrome develops in about 40% of patients who recover from TEN. Seventy-seven percent of the patients recovering from a drug-induced TEN, which they had had 2 months to 4 years before, had xerostomia or keratoconjunctivitis sicca, or both. In 55% of the cases there was lymphocytic infiltration of small salivary glands, in 22% of the patients this was identical to that of Sjögren's syndrome. None of the patients had antinuclear antibody.[4]

Three to four months after the acute phase of drug-induced TEN presented by the patient described here, she began to develop xerophthalmia, xerostomia, cutaneous xerosis and steatorrhea with a severe weight loss.

Other exocrine glands may be involved in Sjögren's syndrome besides the lacrimal and salivary glands. Recipients of allogeneic bone marrow grafts with chronic graft-versus-host disease develop a disorder closely resembling Sjögren's syndrome.[12] Those patients develop xerostomia or keratoconjunctivitis sicca, or both, about one year after receiving their bone marrow grafts. They do not have recurrent parotid gland enlargement, antibodies to extractable nuclear antigens or rheumatoid factor. It seems that chronically activated lymphocytes generated in graft-*vs*-host disease home, for unknown reasons, in on the exocrine glands and destroy them.[13]

The abnormalities of liver function tests were explained by the presence of histopathological features of nonspecific reactive hepatitis. Nonspecific reactive hepatitis can be seen in a wide variety of clinical settings, including those in which the liver may not be primarily involved. Moreover, associated abnormalities of liver function, reflected predominantly by biochemical rather than by clinical signs and symptoms of hepatitis, have been described in drug-induced TEN,[7] in some cases of Sjögren's syndrome[14] and in acute and chronic graft-versus-host disease.[15]

It is generally assumed that TEN is an immunologically mediated disease induced by drug-modified self-proteins,[5] based on the association between TEN and graft-versus-host disease,[2,3] the occurrence of sicca syndromes as sequelae in patients with TEN[4] and the reports of immunoreactants in the skin[16] as well as the altered lymphocyte subsets in peripheral blood[17] and in the inflammatory infiltrate.[18]

We present a case of fulminant drug-induced TEN after metamizole, that 3 months later progressively developed xerophthalmia, xerostomia, cutaneous xerosis and pancreatic exocrine insufficiency. The data presented here suggest that the drug (metamizole) may have triggered a graft-versus-host disease-like mechanism and give support to the immunological origin of toxic epidermal necrolysis.

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