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Kluger, Nicolas

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Cutaneous granulomas caused by subcutaneous injections of leuporelin acetate

Granulomes cutanés après injections sous-cutanées d'acétate de leuproréline

Leuporelin acetate (or leuprolide) is a luteinising hormone-releasing hormone (LH-RH) agonist indicated in the treatment of prostate and breast cancer, endometriosis, uterine leiomyomas and precocious puberty [1]. Polymer-delivered subcutaneous or intramuscular injectable depot formulations are currently used. We report on a new case of cutaneous granulomatous reactions at the injection site associated with an eczematous rash on the body.

Observation

A 82-year-old man with a notable cardiovascular history (hypertension, coronary artery disease and bypass surgery, lower limb

arteriopathy, atrial fibrillation, dyslipidemia) and atrophic gastritis was commenced injections of leuporelin acetate 11.25 mg (Procren depot PDS, Abbvie Oy, Finland) every 3 months in October 2015 for prostate cancer. In November 2016, he started to present erythematous patches on the trunk, back and limbs for which he was referred to us one month later. At presentation, physical examination revealed an erythematous patch of 15 cm on the right side of the abdomen located at the LH-RH injection (figure 1A) within which an asymptomatic and firm infiltration of the size of a thumb could be palpated as well as eczematous patches on the back and the limbs (figure 1B). The patient was aware that he had such reaction on injection sites. He attributed himself the present lesion to an "improper technique". A biopsy of the abdominal lesion revealed epithelioid and giant-cell granulomas with dense fibrosis and some necrosis in the dermis under an acanthotic epidermis with parakeratosis (figure 2A). Foreign bodies made of round translucent microspheres were seen within giant cells (figure 2B). PAS-diastase staining was negative. There was no metastatic tumor. A biopsy of an eczematous lesion of the thigh confirmed the diagnosis of eczema. Laboratory tests revealed a previously known and

FIGURE 1

A. Erythematous nodule on the abdomen at the site of leuporelin injection. B. Eczematous patches on the lower limbs. C. Nodule on the lower abdomen and nummular eczema on the abdomen. D. Easily palpable firm infiltration

FIGURE 2

A. Granulomatous reaction in the dermis with numerous giant cells and numerous translucent round microspheres (hematoxylin-eosin, $\times 10$). B. Foreign body multinucleated giant cell containing vacuoles (hematoxylin-eosin, $\times 40$)

stable normocytic anemia (hemoglobin, 11.3 g/dL) with no other anomaly. C-reactive protein was within normal range. The patient had a moderate reduced kidney function (DFG 45 mL/min/1.73m², stage 3A). Other pertinent laboratories included normal angiotensin-converting enzyme (40; N < 70), while lysozymes were slightly elevated 14.9 mg/L (N < 12). Interferon-gamma release assay for *Mycobacterium tuberculosis* was negative. Highly potent topical steroid (betamethasone, 1 mg/g) were applied daily on the skin. Upon follow-up in May 2017, the eczematous rash had improved albeit it was still present (figure 1C). Previous subcutaneous nodules disappeared, while a new one occurred after the last injection of LH-RH in March 2017 (figure 1D). The patient history, clinical findings, and histopathology were in favor for leuporelin acetate induced granulomatous reaction and eczema. Sarcoidosis and tuberculosis were ruled out. Rapidly growing mycobacterial infection was judged unlikely. We suggested to the patient and treating physician to either try proper injections, deeper intramuscularly or if necessary to switch to another anti-androgenic treatment.

Discussion

Cases of leuporelin acetate-related granulomas have been reported in the literature [1–8], mainly in Japan [8]. However, the incidence of this side effect is not known. In their series of 335 patients, Kawai et al. [8] found that a "rash" at the site of injection occurs in less than 4% of the patients. In Finland, this side effect is not specifically mentioned among the list cutaneous adverse event in the official Pharmaca Fennica [10]. Granulomas appear usually weeks to months after 1,7 to 2,4 injections [8]. They present as subcutaneous, firm, well-defined, non-adherent to the underlying tissue and non-tender nodules.

The skin on surface is usually normal [2,7], slightly erythematous or inflammatory [3,4,8], sometimes even ulcerated with suppuration [6,8]. Interestingly, granulomas do not always relapse after each injection [6]. The physiopathogeny of the lesions is not totally known, but the most accepted hypothesis is that of a foreign-body reaction against polylactic acid polymers [4], even though some authors reported reactions with leuporelin without polymers [9]. Granulomas develop more rapidly and easily in case of subcutaneous injections (or if the injections are performed too superficially) [4], as illustrated by the numerous cases from Japan, where subcutaneous injection is the method of choice [1,3]. They also mainly occur with the 11.5 mg formulation that is administrated every 3 months [3,8]. Management of such reactions includes suggesting using preferably an intramuscular administration. Besides, several authors have stressed that local reactions may impair LH-RH absorption and efficacy [1,5]. Therefore, a switch to another therapy, such as goserelin, can be recommended.

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Nicolas Kluger, Sonja Hahtola, Tea Lempinen, Leila Jeskanen

University of Helsinki, Helsinki University Central Hospital, Departments of dermatology, allergology and venereology, Meilahdentie 2, PO Box 160, 00029 Helsinki, Finland

Correspondence: Nicolas Kluger, University of Helsinki, Helsinki University Central Hospital, Departments of dermatology, allergology and venereology, 00029 Helsinki, Finland
nicolas.kluger@hus.fi

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Acute necrotic pancreatitis: A rare and not always fatal cause of central pontine myelinolysis

Pancréatite aiguë nécrotique : une cause rare et pas toujours létale de myélinolyse centro-pontine

Introduction

Extra and central pontine myelinolysis (CPM) are considered as osmotic demyelination syndromes (ODS) [1]. The most frequent aetiology of central pontine is rapid correction of hyponatremia. In that case, the prognosis is usually known as highly severe. Nevertheless, a few cases without osmolarity disorder are described [2]. Myelinolysis complicating an acute pancreatitis is extremely rare. To our knowledge, only 2 cases have been

described in the literature [3,4]. Mechanisms involved and outcomes of CPM in a context of acute pancreatitis are still unknown. We herein describe, following the CARE guidelines, the case of a patient admitted for central myelinolysis in a context of acute pancreatitis without hyponatremia [5].

Case report

A 31-year old man, with a past medical history of chronic alcoholism, was admitted with severe abdominal pain and vomiting, revealing an acute pancreatitis. Upon admission, neurological examination was unremarkable. Laboratory findings showed an increased serum lipase level at 666 UI/L, sodium level at 133 mmol/L, potassium at 3.50 mmol/L and C reactive protein elevated at 55. Liver enzymes were discreetly increased less than twice normal and bilirubin was normal. Computed tomography (CT) of abdomen and pelvis has confirmed the diagnosis of acute non-haemorrhagic pancreatitis. Considering the medical history of chronic alcoholism with several alcohol rehabilitations, the persistent elevated mean corpuscular volume and the hepatic steatosis seen on CT, the alcoholic origin of this pancreatitis was retained. More, there was no dilation of the bile ducts or cholestasis.

The patient received conservative treatment and was placed on a low-fat diet. In the absence of hemodynamic failure, the patient did not receive any massive intravenous fluid during the initial care that could have corrected a former hyponatremia. One week after admission, the patient rapidly deteriorated with a spastic quadriparesis and disturbance of consciousness. The neurological examination revealed dysarthria, facial diplegia, dysphagia and bilateral Babinski sign. There was no oculomotor abnormality.

The lipase had returned to normal (45 U/L) and the sodium level, assessed extensively with daily control since the admission, had remained within the normal range. A cerebral MRI was performed revealing a hypointense T1 signal without enhancement after contrast, hyperintense fluid attenuated inversion recovery (FLAIR) signal, well limited and symmetric in the central portion of the pontine base (figure 1). This lesion was associated with discrete lesion in the left striatum. Given the very limited nature of the lesion in the central part of the brain stem, without oedema or infiltrating character, or without criteria for spatial dissemination, we have ruled out diagnosis of glioma of the brainstem, multiple sclerosis or infection as a listeriosis. Final diagnosis retained was extra and central pontine myelinolysis. He was treated in intensive care unit with conservative care, including thiamine supplement and elective intubation for airway protection during 6 days. The patient remained in critical condition for several weeks, leading to a tracheotomy decision after a week. Repeat MRI at one month showed increased size of the lesions in the pons (figure 2). The patient's condition improved spontaneously after 3 weeks with recuperation of a frank mobilization of all members but persistent