Parkinsonism and Related Disorders 65 (2019) 279–281

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Correspondence

Severe abdominal panniculitis in a patient treated with continuous subcutaneous apomorphine infusion

ARTICLE INFO

Keywords:
Apomorphine
Panniculitis
Skin nodules
CSAI

We are reporting the case of a 53-year-old patient with a 10-year history of PD admitted at our Hospital after multiple masses localized in his abdominal wall. His previous records were unremarkable besides past treated syphilis. He had been initially treated with levodopa/benserazide and dopamine agonists, although the latter had to be discontinued due to impulse control disorder that subsequently resolved. Over time, he required continuous subcutaneous apomorphine infusion (CSAI) due to intractable motor fluctuations. However, he had missed a number of follow-ups prior to being admitted.

On admission, abdominal indurations were seen at the examination (Fig. 1, top). A peripheral blood test was performed showing no remarkable findings, including white cell count within the normal range. An abdominal MRI was performed, showing several foci of edematous and trabecullated subcutaneous cellular tissue. A biopsy showed panniculitis with acute mixed inflammatory reaction with fat tissue necrosis (Fig. 1, bottom). Cultures were positive for *Staphylococcus aureus*. On discharge, he was withdrawn from CSAI and his dopaminergic treatment was adjusted. Interestingly, his external records were remarkable for a previous admission in a different hospital, in which he also was positive for *Staph. aureus*.

Amongst all the antiparkinsonian drugs in the market, apomorphine has the largest history of use since it was first synthesized by Arppe in 1845. However, it had to overcome a long journey after the first attempts made by Anderson in 1935 until its approval by FDA in 2004 for Parkinson's disease (PD) [1] and the most recent TOLEDO trial, that provides first-ever evidence from a double blind, placebo controlled study of its safety and efficacy [2]. Skin side effects, mostly manifested as skin nodules; with more severe forms being rare are the adverse phenomena most frequently encountered in clinical practice.

Apomorphine is administered subcutaneously either by intermittent injection or continuous infusion for PD patients whose motor fluctuations remain under poor control despite optimal oral or transdermal pharmacological treatment. In spite of its proven effectiveness in moderately-advanced stages of PD, skin side effects can be troublesome (and are much more frequent than other side effects such as hemolytic anemia), often setting a drawback for many clinicians.

Indurations on infusion sites, termed as skin nodules, develop with time in the vast majority of the patients, with the prevalence reported being as high as 92%, albeit more severe forms prompting discontinuation of treatment happen in only 3% of the patients.

In a large study involving several tertiary care centers in Spain, 4 patients out of a total of 166 (0.02%) who received CSAI therapy had to be withdrawn from the drug. Given that, in that study, 87% of the patients presented local adverse reactions of any severity and only an extremely small number of them prompted discontinuation, the former have been contemplated as well-tolerated, low-risk side effects [3]. In the TOLEDO trial, only one patient was withdrawn due to skin side effects. Skorvanek et al. proposed several non-pharmacological measures in their review of the relationship between skin and PD [4].

Causative mechanisms are yet to be clearly elucidated. It must be taken in account that literature is scarce on pathologically proven panniculitis. The 1989 report by Acland, K. M., et al. included 10 patients who underwent biopsy showing in half of the cases eosinophilic infiltrates. However, neither raised Ig E levels nor other features clearly pointing towards a hypersensibility –related pathogenia were found. Although theoretically, opioid-related drugs can induce mast cell degranulation, there were no findings of increased number or degranulated mast cells at the time [5]. Other factors such as local cell toxicity, vasoconstriction and worsening of pre-existing coagulation have been hypothesized to play a role.

In our opinion, the rationale for performing a biopsy should merely be ruling out alternative diagnosis or relevant complications, therefore not being needed in the majority of cases. Irregular follow up and poor hygiene often complicate the clinical picture, as it might have happened to our patient.

Apomorphine is an effective treatment for advanced PD. Dermatologic side effects, although generally mild, must be carefully addressed in all patients, who should receive adequate information about the risks of discontinuing follow-up and proper nursing cares. Thorough monitoring of adverse effects is relevant for PD patients receiving invasive therapies, being this particularly true for patients undergoing CSAI. Doctors and nurses must work closely with these pa-

https://doi.org/10.1016/j.parkreldis.2019.06.011
Received 27 March 2019; Received in revised form 4 June 2019; Accepted 10 June 2019

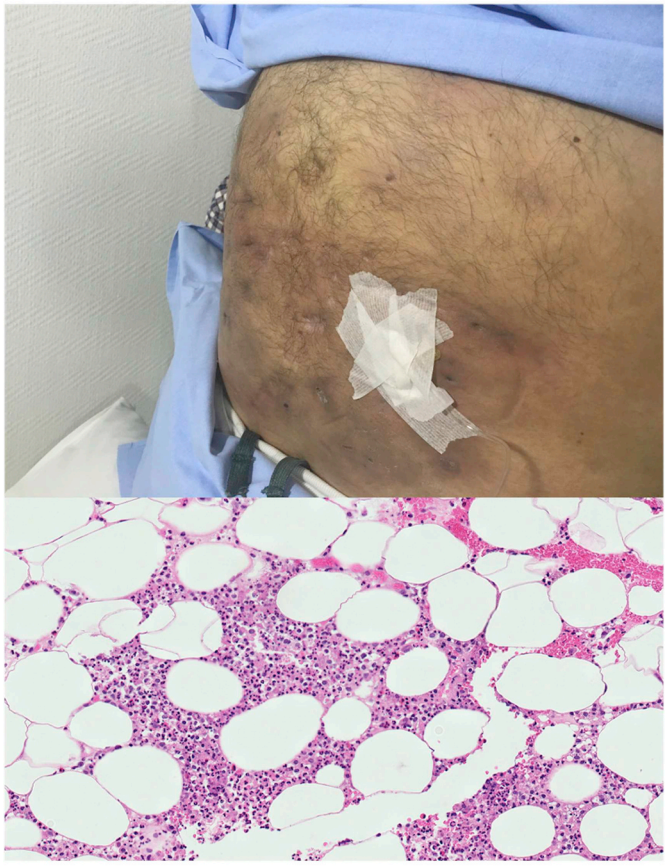

Fig. 1. Top: Multifocal masses are present at infusion sites on the patient's abdominal wall. Bottom: Hematoxilin-eosin staining showing the presence of lymphocites, neutrophils and eosynophiles infiltraiting the subcutaneous cellular tissue. Small-size adypocites entangled with inflammatory cells represent ongoing fat tissue necrosis.

tients in order to reduce the incidence and severity of skin adverse effects. Poor compliance to follow-ups poses, in our opinion, substantial risk for severe complications, therefore, treatment discontinuation might be required.

Author roles

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript: A. Writing of the first draft, B. Review and Critique.

A.Q.C.: 1A, 1B, 1C, 3A
C.F.F: 1A, 1C
J.d.V.F.: 1A, 1 B, 1C, 3A, 3B
J.S.G.: 1C
J.F.A: 1C
P.J.G.-R.: 1A, 1B, 1C, 3B

Financial disclosures

Funding Sources and Conflicts of Interest: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the previous 12 months: Querejeta-Coma A. has received travel grants by Sanofi, UBC and Pfizer; Pedro J. García-Ruíz received personal compensation as a consultant/scientific advisory board from Italfarmaco, Britannia, Bial and Zambon and speaking honoraria from Italfarmaco, Zambon, Allergan and Abbvie.

Submission declaration

The authors declare that the present work has not been published previously, it is not under consideration for publication elsewhere and has been approved by all the authors. Preparation and submission of the article have been made according to the rules regarding case reports of our hospital.

All authors have materially participated in the writing of this draft.

Ethical compliance statement

The WMA Declaration of Helsinki guidelines regarding Ethical Principles for Medical Research were followed on the development of this work.

Verbal consent from the patient was obtained at the time of image acquisition.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

References

[1] Manon Auffret, Sophie Drapier, Marc Vérin, The many faces of apomorphine: lessons from the past and challenges for the future, Drugs R (2018) 1–17.
[2] Regina Katzenschlager, et al., Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial, Lancet Neurol. 17 (9) (2018) 749–759.
[3] Garcia-Ruiz, J. Pedro, et al., Efficacy of long-term continuous subcutaneous apomorphine infusion in advanced Parkinson's disease with motor fluctuations: a multicenter study, Mov. Disord. 23 (8) (2008) 1130–1136.
[4] Matej Skorvanek, Kailash P. Bhatia, The skin and Parkinson's disease: review of clinical, diagnostic, and therapeutic issues, Mov. Disor. Clin. Prac. 4 (1) (2017) 21–31.
[5] K.M. Acland, et al., Panniculitis in association with apomorphine infusion, Br. J. Dermatol. 138 (3) (1998) 480–482.

A. Querejeta-Coma*, C. Feliz-Feliz, J. Del Val
Neurology Department, Hospital Fundación Jiménez Díaz-Ute, Madrid, Spain
E-mail address: aquerejeta@quironsalud.es (A. Querejeta-Coma).

J. Sánchez-García, J. Fortes-Alen
Anatomic Pathology Department, Hospital Fundación Jiménez Díaz-Ute, Madrid, Spain

Pj Garcia-Ruiz
Neurology Department, Hospital Fundación Jiménez Díaz-Ute, Madrid, Spain

* Corresponding author. Department of Neurology, Hospital Fundación Jiménez Díaz, Av. Reyes Católicos 2, 28040, Madrid, Spain.