European Journal of Cancer 110 (2019) 71–73

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Letter to the Editor

Mitochondrial myopathy associated with anti-programmed cell death 1 therapy

Tony Ibrahim [a,*], Clovis Adam [b], Emilie Routier [c], Abdelhamid Slama [d], Caroline Robert [c,e,**]

[a] *Medical Oncology Department, Gustave Roussy cancer campus, 114, Rue Edouard Vaillant, 94 800, Villejuif, France*
[b] *Neuropathology Department, Bicêtre Hospital, Le Kremlin-Bicêtre, France*
[c] *Dermatology Unit, Oncology Department, Gustave Roussy cancer campus, Villejuif, France*
[d] *Biochemistry Department, Bicêtre Hospital, Le Kremlin-Bicêtre, France*
[e] *Paris-Sud University, Kremlin Bicêtre, France*

Received 12 December 2018; accepted 2 January 2019
Available online 14 February 2019

Dear Editor,

Immune therapy inhibiting programmed cell death 1 (PD1) has been a major breakthrough in modern cancer therapy and is associated with a unique immune-driven toxicity profile [1]. We present two cases of patients with metastatic melanoma who developed secondary mitochondrial myopathy which was suspected to be induced by anti-PD1 monoclonal antibodies (mAb).

The first patient was a previously healthy 44-year-old woman, while the second patient was a previously healthy 70-year-old man. None of them took any medication. The tumour harboured BRAF V600E mutation only in the first patient who was treated with first-line dabrafenib and trametinib combination. On progression, nivolumab was started at 3 mg/kg IV q2 weeks in the first patient and pembrolizumab at 2 mg/kg IV q3 weeks in the second patient. They both developed grade II generalised muscle weakness (according to the Common Terminology Criteria for Adverse Events [CTCAE] v4.03) after 2 and 11 cycles of immune therapy, respectively. The physical examination was unremarkable except for a symmetrical proximal muscle weakness in all four limbs, with a limb-girdle distribution but without muscle atrophy. The serum creatine kinase (CK) level was in the normal range, and thorough laboratory testing did not reveal any abnormality, including screening tests for endocrine disorders and serological testing for myositis-specific and associated autoantibodies. Signs of proximal myopathy were detected on electromyogram (EMG). Muscle biopsy examination did not show lymphocyte infiltration but revealed signs of mitochondrial myopathy, with atrophic and irregular size muscle fibres associated with COX-negative and ragged red fibres (RRF). Electron microscopy showed mitochondrial number variation and evidence of abnormal mitochondrial crests (Fig. 1). Mitochondrial respiratory chain (RC) enzymatic activities were normal in the first patient, whereas in the second patient, RC complexes I and IV were in the lower range. Analysis of mitochondrial DNA (mtDNA) in the first patient

* *Corresponding author*.
** *Corresponding author*: Dermatology Unit, Oncology Department, Gustave Roussy cancer campus, Villejuif, France.
E-mail addresses: tony.ibrahim@gustaveroussy.fr (T. Ibrahim), clovis.adam@aphp.fr (C. Adam), emilie.routier@gustaverousssy.fr (E. Routier), abdel.slama@aphp.fr (A. Slama), caroline.robert@gustaverousssy.fr (C. Robert).

https://doi.org/10.1016/j.ejca.2019.01.001

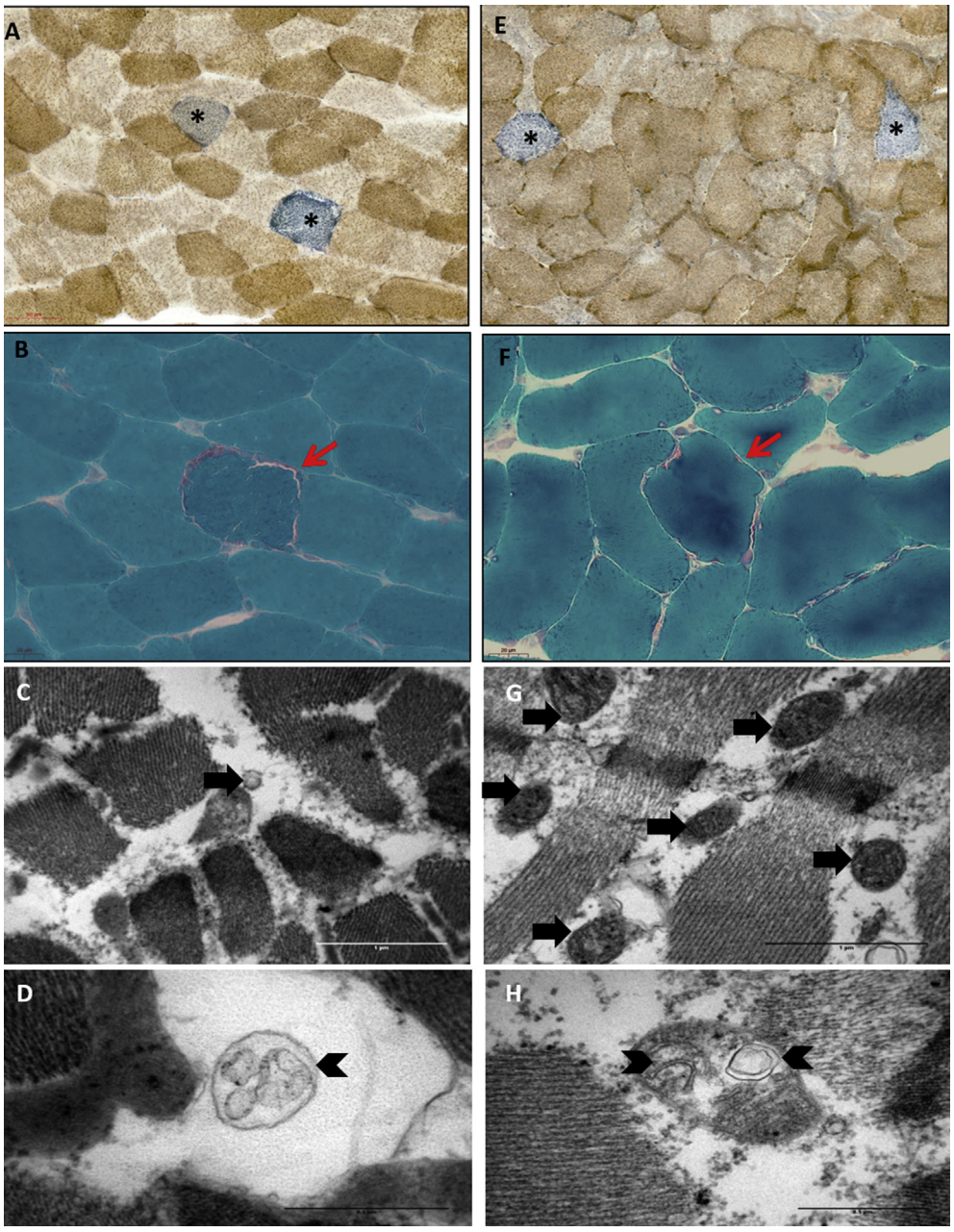

Fig. 1. Light microscopy showing COX-SDH staining with COX-negative fibres (asterix in panel A-case 1 and panel E-case 2) and Gomori trichrome stain with ragged red fibres (red arrow in panel B-case 1 and panel F-case 2). Electron microscopy showing mitochondrial number variation with a decreased number in case 1 (black arrow in panel C) and an increased number in case 2 (black arrow in panel G), associated with abnormal mitochondrial crests (arrowheads in panel D-case 1 and panel H-case 2). COX-SDH, cytochrome C oxidase/succinate dehydrogenase. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

showed a reduction in the copy number (46% of the normal range) and sequencing revealed a rare single nucleotide variant (m.14434C > T), predicted to be a polymorphism. In the second patient, mtDNA sequencing revealed a heteroplasmic mutation (m.15769A > C) in the cytochrome B gene, present only in fibroblasts. This mutation is predicted to be damaging, but mitochondrial complex III was normal.

In both cases, immune therapy was discontinued, and symptoms were markedly reduced. The first patient had rapid tumour progression and died thereafter. In the second patient, pembrolizumab was reintroduced after 6 weeks of discontinuation, but muscle weakness reappeared 5 days after the first cycle. Thus, treatment was definitely interrupted. He maintained a partial response, according to the immune-related response

criteria, for 6 months but died thereafter because of tumour progression.

In fact, muscle toxicity has been reported in patients receiving immune therapy [1]. Although isolated myalgia is the most described finding, cases of inflammatory and necrotising myositis have been documented [2]. Mitochondrial dysfunction in skeletal muscle has never been reported. In fact, the diagnosis of the secondary mitochondrial myopathy is difficult to confirm because there are no clear and obvious diagnostic criteria [3]. Still, a beam of arguments can guide the diagnosis and includes the following findings: a normal CK level, signs of myopathy on EMG, absence of causative medication, and unremarkable laboratory investigation including screening tests for endocrinology disorders and serological testing for autoimmune myositis. Muscle biopsy is the most useful procedure for establishing the diagnosis and excluding other etiologies [4]. The absence of lymphocyte infiltration and the detection of signs of mitochondrial damage on light and electron microscopy (Fig. 1) supported the diagnosis of mitochondrial myopathy in our two patients. The causal relationship between the anti-PD1 therapy and the mitochondrial myopathy is suggested by the kinetics of the events, with the emergence of symptoms on the introduction of immune therapy, their resolution after its discontinuation and, mostly, the relapse of symptoms on reintroduction of the anti-PD1 mAb as in the second patient. All these findings are strong arguments in favour of drug responsibility. One hypothesis is that mitochondrial dysfunction may be the result of increased energy consumption secondary to the overstimulation of the immune system, which surpasses the body's ability to generate ATP. As a result, the cells that are most dependent on mitochondria for their energetic functioning, especially muscle fibres, would be the most affected. Individual susceptibility to develop this adverse event after immunotherapy could depend on the mitochondrial genetic material. Indeed, some mtDNA mutations, as the one detected in the second patient, may not affect the daily activity but could be unmasked in stressful situations [5]. It is unclear whether non-deleterious polymorphisms of mtDNA, such as the case of the first patient, could also be a factor of susceptibility to this type of toxicity.

In conclusion, we report the first two cases in the literature of the secondary mitochondrial myopathy associated with anti-PD1 therapy. Further studies would help to assess the frequency of this association and to unveil its underlying mechanisms.

Conflict of interest statement

None declared.

Acknowledgements

The authors would like to thank doctor Libenciuc Cristina, doctor Pauline Gaignard, doctor Olivier Lambotte, and dr Cécile Cauquil for their assistance in the follow up of the patients.

References

[1] Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol 2016; 13:473–86. https://doi.org/10.1038/nrclinonc.2016.58.

[2] Vallet H, Gaillet A, Weiss N, Vanhaecke C, Saheb S, Touitou V, et al. Pembrolizumab-induced necrotic myositis in a patient with metastatic melanoma. Ann Oncol 2016;27:1352–3. https://doi.org/10.1093/annonc/mdw126.

[3] Niyazov DM, Kahler SG, Frye RE. Primary mitochondrial disease and secondary mitochondrial dysfunction: importance of distinction for diagnosis and treatment. Mol Syndromol 2016;7:122–37. https://doi.org/10.1159/000446586.

[4] Parikh S, Goldstein A, Koenig MK, Scaglia F, Enns GM, Saneto R, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. Genet Med 2015;17:689–701. https://doi.org/10.1038/gim.2014.177.

[5] Carelli V, La Morgia C. Clinical syndromes associated with mtDNA mutations: where we stand after 30 years. Essays Biochem 2018;62:235–54. https://doi.org/10.1042/EBC20170097.