Facial lipodystrophy after immunotherapy with Nivolumab

Dear Editors,

the use of immune checkpoint inhibitors such as pembrolizumab and nivolumab, two antibodies directed against programmed death-1 (PD-1), and ipilimumab, an antibody against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), has fundamentally changed the therapy and prognosis of malignant melanoma [1]. In addition to the treatment of patients with unresectable metastatic stage III or IV melanoma, PD-1 inhibitors have also been approved for adjuvant treatment after complete tumor resection [2]. This is the potentially serious immune-mediated adverse events that may be persistent. Thus, dermatitis, thyroiditis, colitis, pneumonitis, hepatitis, and hypophysitis, among others, can be observed [3–5]. To ensure safe handling of this group of substances, early recognition and treatment of these adverse events is necessary.

We report on a 41-year-old female patient who underwent excision of a superficially spreading malignant melanoma with a tumor thickness of 2.0 mm on the left thigh in November 2017. After detection of a 3 mm measuring metastasis in the sentinel lymph node, positron emission tomography (PET) imaging of the body and magnetic resonance imaging (MRI) of the brain were performed. No evidence for metastasis of the melanoma was found in either examination. In accordance with the 2017 guideline, an inguinal lymph node dissection was performed on the left side. No tumor cells were detected in the excidate by histopathological examination. Subsequently, in April 2018, we initiated adjuvant immunotherapy with nivolumab (240 mg every two weeks). This treatment was well tolerated by the patient over the entire therapy period of twelve months. Thankfully, to date, in biannual follow-ups by cross-sectional imaging the patient has remained tumor-free.

In June 2019, a few weeks after completion of adjuvant therapy with nivolumab, the patient noticed an induration around both her cheeks. She also noticed a gradual recession of the eyes into the sockets. Physical examination revealed a marked reduction in subcutaneous fatty tissue on both cheeks and temples, as well as enophthalmos, consistent with partial lipodystrophy (Figure 1). In addition to drugs (antiretrovirals, insulin), infections, surgical procedures, radiation therapy, autoimmune diseases such as systemic lupus erythematosus, and complex genetic diseases may cause partial lipodystrophy. After ruling out these diseases, we diagnosed our patient with immune-mediated localized lipodystrophy as an adverse event due to adjuvant therapy with the PD-1 inhibitor. Blood levels of cholesterol and triglycerides, HbA1c level, and antinuclear antibodies were normal. A therapy attempt with prednisolone (daily 1 mg/kg body weight orally for four weeks) did not improve the symptoms.

Lipodystrophy is a general term for a group of disorders that are characterized by loss or maldistribution of adipose tissue [6]. Hereditary variants are distinguished from acquired variants and generalized variants from partial variants [7]. In acquired generalized lipodystrophy (AGL), varying degrees of adipose tissue loss occur over months to years throughout the body. Fat metabolism and metabolic activity of the fatty tissue are impaired. As a consequence, ectopic fat deposits in liver and muscles as well as severe metabolic imbalances with hypertriglyceridemia and diabetes mellitus may result. Additionally, panniculitis, hirsutism, acanthosis nigricans, hypogonadism, and autoimmune disorders may also occur in AGL. Partial lipodystrophy is characterized by localized loss of fatty tissue, especially in the face, neck, arms, thorax, and upper abdomen [7, 8]. Compared to the generalized form, metabolic effects are observed much less frequently and to a lesser extent. Therapy of lipodystrophies is often frustrating. For the generalized form, treatment of the accompanying metabolic symptoms such as hypertriglyceridemia or diabetes mellitus is of primary concern [8]. In addition, especially in the case of cosmetically disturbing and stigmatizing changes in the face, surgical intervention is possible, for example by insertion of an implant [9]. In patients with difficult-to-control lipodystrophy and concomitant hypertriglyceridemia or diabetes mellitus, subcutaneous therapy with metreleptin, a leptin analog, has been approved in the United States [10]. Since subcutaneous loss of fatty tissue

Figure 1 Lipodystrophy of the cheeks and enophthalmos twelve weeks following twelve months of adjuvant therapy with nivolumab.
results in a deficiency of the signaling molecule leptin, which plays a critical role in the regulation of energy homeostasis. Substitution of leptin has been shown to significantly improve metabolic symptoms [11]. Hyperlipidemia has been observed in 80–90% of the described cases of acquired lipodystrophy after therapy with a PD-1 antibody. To date, this adverse event, which developed both during and after cessation of PD-1 inhibitor therapy, has mainly affected women. No reports of successful treatment of this rare immune-mediated effect have been published to date. Currently reported cases are summarized in Table 1 [12–16].

The diversity of immune-mediated adverse events poses both a diagnostic and therapeutic challenge. The publication and reporting of rare, adverse events in the appropriate registries will help to further improve handling of this group of substances. Providing patients with detailed information on adverse effects, which may be irreversible, is necessary to enable informed decision making and to further improve the acceptance of adjuvant immunotherapy [17].

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**Conflict of interest**

None.

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**Table 1** Previously described cases of acquired lipodystrophy after therapy with a PD-1 inhibitor.

|                | Haddad et al. | Kruschewsky et al. | Jehl et al. | Bedrose et al. | Gnanendran et al. | Presented case |
|----------------|---------------|--------------------|------------|---------------|------------------|---------------|
| Age            | 47            | 57                 | 62         | 67            | 34               | 41            |
| Sex            | Female        | Female             | Male       | Female        | Female           |               |
| Tumor entity   | Melanoma      | Renal cell carcinoma | Melanoma | Melanoma | Melanoma | Melanoma |
| Medication     | Pembrolizumab | Nivolumab           | Nivolumab | Pembrolizumab | Nivolumab | Nivolumab |
| Duration of therapy until diagnosis | 2 months | 2 months | 18 months | 6 weeks | 9 months | 13 months |
| HbA1c          | 6.1% (43 mmol/mol) | 10.5% (91 mmol/mol) | 11.4% (101 mmol/mol) | 7.2% (55 mmol/mol) | 5.1% (34 mmol/mol) | 5.4% (35 mmol/mol) |
| Diagnosis      | Acquired generalized lipodystrophy | Acquired generalized lipodystrophy | Acquired generalized lipodystrophy | Acquired generalized lipodystrophy | Acquired generalized lipodystrophy | Acquired generalized lipodystrophy |

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