Acquired Generalized Lipodystrophy: A New Cause of Anti-PD-1 Immune-Related Diabetes

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OBJECTIVE

Anti–programmed cell death-1 (anti-PD-1) antibodies have revolutionized advanced cancer therapy. Anti-PD-1 therapy is responsible for immune-related adverse events, with frequent endocrine manifestations, including acute-onset type 1 diabetes. Acquired generalized lipodystrophy (AGL) is a rare disease, believed to be immune mediated, characterized by loss of adipose tissue and insulin resistance–associated complications.

RESEARCH DESIGN AND METHODS

We describe the first reported case of AGL induced by immune checkpoint therapy.

RESULTS

A 62-year-old woman with metastatic melanoma treated with nivolumab was referred for major hyperglycemia, hypertriglyceridemia, and nonalcoholic steatohepatitis. She had presented with a rapidly progressive generalized loss of subcutaneous adipose tissue. Diabetes was associated with severe insulin resistance and undetectable plasma leptin. Subcutaneous biopsy revealed atrophic adipose tissue infiltrated with cytotoxic $CD8^+$ T lymphocytes and fibrosis.

CONCLUSIONS

AGL is an additional immune-related adverse event of anti-PD-1 therapy that leads to severe insulin resistance–associated complications.

Anti–programmed cell death-1 (anti-PD-1) antibodies have revolutionized advanced cancer therapy. However, immune checkpoint therapy also interferes with tolerance to self-antigens, leading to multiorgan autoimmune-related adverse events. The incidence of anti-PD-1 immune-related endocrine side effects has been estimated to be 5–10% and these side effects include thyroid disorders, hypophysitis, adrenal insufficiency, and insulin-requiring diabetes (1).

Acquired generalized lipodystrophy (AGL) is a rare disease characterized by loss of subcutaneous adipose tissue with severe insulin resistance leading to diabetes, hypertriglyceridemia, and nonalcoholic steatohepatitis. Twenty-five percent of AGL cases are associated with autoimmune diseases (2). We describe the first case of AGL occurring during the course of immune checkpoint therapy using nivolumab, a fully human monoclonal antibody targeting PD-1.

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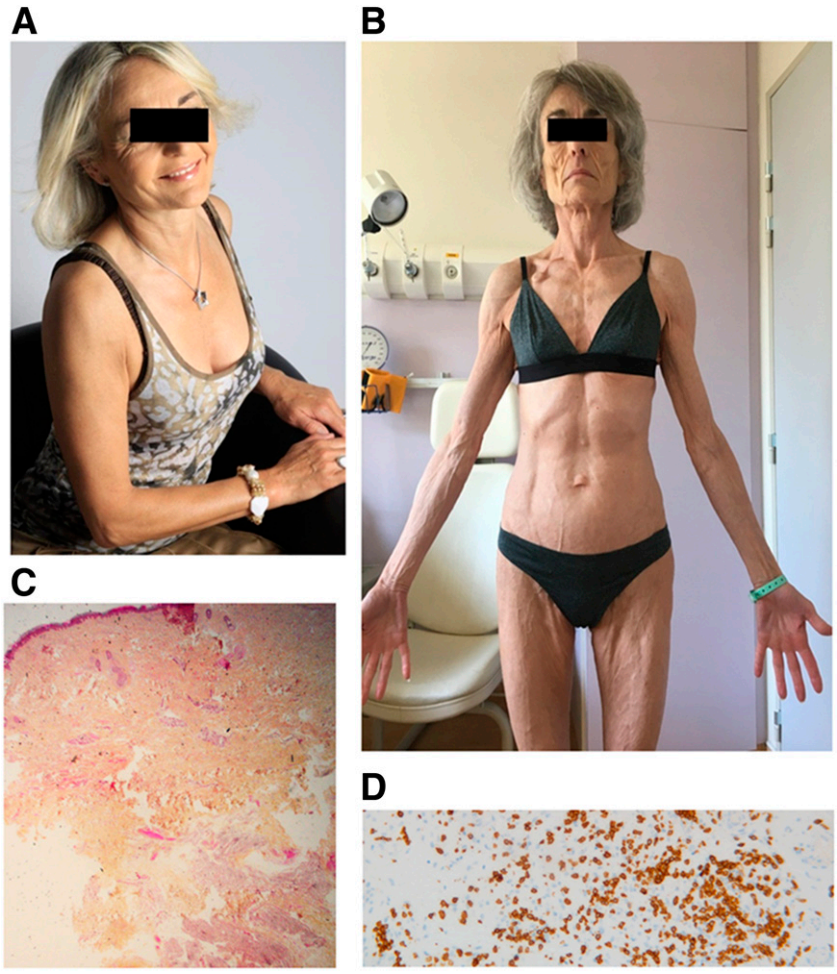

Figure 1—Patient's morphotype at age 55 years (*A*) and at age 62 years, 3 months after discontinuation of an 18-month nivolumab therapy (*B*). Histopathological study of a subcutaneous biopsy of the gluteal region, hematoxylin, phloxine, and saffron staining: original magnification ×12.5 (*C*) and ×100 (*D*). Lobules of adipose tissue were completely disrupted by fibrosis, with proliferation of capillaries and an extensive inflammatory infiltrate. Immunohistochemistry revealed cytotoxic T lymphocytes ($CD3^+CD8^+$), one-third of which expressed cytotoxic factors (granzyme B, perforin, T-cell–restricted intracellular antigen-1).

CASE REPORT

A 62-year-old woman was referred to our endocrinology department with severe hyperglycemia. She was diagnosed at age 50 with a superficial spreading melanoma of the shoulder, which was treated with surgery. Ten years later, she developed an acute confusional state revealing brain, pulmonary, and liver metastases with V600E *BRAF* somatic mutation. Nivolumab therapy was initiated and led to a partial tumor response. After 18 months of treatment, the patient developed a severe and rapidly progressive weight loss with increased liver enzymes (Supplementary Table 1). A major liver steatosis, hitherto unknown, was revealed by abdominal CT scan (Supplementary Fig. 1) and confirmed by biopsy (steatosis score 3, activity score 3/4, fibrosis score 1b). Autoimmune and viral hepatitis were ruled out. Nivolumab therapy was then discontinued. One month later, the patient presented with polyuria, polydipsia, and further worsening of weight loss despite the development of a severe hyperphagia. She was admitted to our endocrinology department with nonketotic diabetes (glucose 24.9 mmol/L, HbA_{1c} 11.4% [101 mmol/mol]). Her weight was 46.9 kg (BMI 16.8 kg/m^2).

Clinical examination demonstrated generalized lack of subcutaneous fat with prominent muscularity (Fig. 1*A* and *B*). Lipoatrophy, which developed during the past few months as reported by the patient, was striking in the face, with prominent zygomatic arches; in the neck, shoulders, and subclavicular areas; and in the trunk and limbs, with prominent veins. Skin lesions of acanthosis nigricans were present in axillary folds. The total body fat content, assessed by DEXA, was low (16.2% [normal range 27–30%]), and plasma leptin was undetectable.

Type 1 diabetes–related autoantibodies (anti-GAD, islet antigen 2, and zinc cotransporter 8) were negative, although the patient exhibited a class II HLA DR4 haplotype (DRB1*04 DQA1*03 DQB1*03:02). Abdominal CT scan did not reveal any pancreas abnormality, and serum lipase was within the normal range. Fasting plasma insulin, C-peptide, HOMA of insulin resistance, and triglyceride-glucose insulin resistance index were strongly increased (40 mIU/L, 2.3 nmol/L, 44.3, and 6.19, respectively) as were serum triglycerides (6.4 mmol/L), whereas HDL cholesterol and plasma adiponectin were low (Supplementary Table 1). Lipoatrophy and insulin resistance–associated metabolic abnormalities were absent at the time of nivolumab initiation (Supplementary Table 1).

A search for serum autoantibodies directed against insulin and insulin receptor and non–organ-specific autoantibodies (antinuclear, anti-SS-A, anti-SS-B, centromere, ribosome, chromatin, Scl-70, Sm and Sm RNP, Jo-1, Rh factor, and antineutrophil cytoplasmic antibody) was negative, and C3, C4, and CH50 complement levels were in the normal range. The patient did not report any familial antecedent of lipoatrophy. Congenital generalized lipodystrophy was ruled out on the basis of the natural course of the disease and the absence of any pathogenic variant in 23 genes associated with lipodystrophy. Prolactin, corticotropic, and somatotropic axes were normal or subnormal (prolactin 8.4 μg/L [normal range 4.8–23 μg/L], fasting plasma cortisol 264 nmol/L, ACTH 20 μg/mL [5–50 μg/mL], IGF-I 85 μg/L [87–194 μg/L]). Gonadotrophin hormones were increased (follicle-stimulating hormone 90.9 IU/L, luteinizing hormone 26 IU/L) and estradiol decreased (<17 pmol/L) in accordance with the patient's postmenopausal status. The thyroid function was controlled with L-thyroxine (thyroid-stimulating hormone 2.7 mIU/L, thyroxine 10.2 pmol/L).

A subcutaneous biopsy of the gluteal region revealed major histological alterations (Fig. 1*C*). The lobular organization of adipose tissue was disrupted by fibrosis

and proliferation of vascular capillaries and by an extensive lymphoid infiltrate mostly composed of $CD8^+$ T cells, which expresses cytotoxic factors (granzyme B, perforin, T-cell–restricted intracellular antigen-1) in one-third of cases (Fig. 1*D*).

A high-dose basal-bolus insulin regimen was initiated (1.6 units/kg/day) in association with adapted diet and metformin. Four months after insulin initiation, HbA_{1c} decreased to 6.2% (44 mmol/mol), body weight increased (7%), bolus of insulin was discontinued, and basal insulin was maintained (0.7 units/kg/day) in association with metformin. At the same time, triglycerides were decreased by 40% but remained twofold above normal range. An informed consent of the patient was obtained for this publication.

CONCLUSIONS

We describe a typical case of AGL that occurred during the course of anti-PD-1 immune therapy. AGL was characterized by a rapidly progressive loss of adipose tissue, leading to leptin deficiency and severe insulin resistance, hypertriglyceridemia, and hepatic steatosis. AGL is a rare disease that is believed to result from immune-mediated destruction of adipocytes (3). Autoantibodies against perilipin-1, the most abundant adipocyte-specific protein that coats lipid droplets, have been recently identified in some patients with AGL (4). While the mechanism of adipocyte destruction is not clearly elucidated in the present case study, it may result from disrupted immunological tolerance to self-antigens secondary to immune checkpoint inhibition, which could lead to aberrant targeting of adipocyte antigens by reactivated T cells. In accordance, histopathological dermal features showed a disorganization of fat lobules with massive infiltration of cytotoxic $CD8^+$ T cells and fibrosis.

Diabetes has been previously reported following PD-1 blockade, although in a very different pathophysiological context. In the majority of reported cases, a fulminant onset of insulin-deficient diabetes with ketoacidosis and a near-normal HbA_{1c} were observed, with one-half of the affected subjects being positive for at least one type 1 diabetes–related autoantibody and 40% for HLA DR4 (5,6). It is speculated that anti-PD-1–related fulminant diabetes is due to a sudden and major activation of β-cell–reactive $CD8^+$ T-cell clones without any contribution of humoral immunity. In such cases, a bihormonal endocrine and exocrine pancreatic failure associated with acute pancreas atrophy has also been reported (7,8). Despite a high-risk HLA class II haplotype for type 1 diabetes, severe hyperglycemia, and recent major weight loss, diabetes in the present patient is characterized by absence of ketosis, severe insulin resistance rather than insulinopenia, and generalized lipoatrophy with major leptin deficiency. Consistently, in AGL, the inability to store lipids in adipocytes induces ectopic fat deposits, leading to whole-body insulin resistance, hypertriglyceridemia, and liver steatosis (2,3,9).

Recombinant human leptin is a relevant treatment option to control metabolic abnormalities associated with generalized lipodystrophy, as acknowledged by the Food and Drug Administration and European Medicines Agency (9–11). However, besides its metabolic roles, leptin also modulates both innate and adaptative immune functions, which could interfere with both autoimmune and oncogenic diseases. Further studies should evaluate the risk-benefit ratio of leptin replacement therapy in anti-PD-1–associated AGL.

In conclusion, AGL should be added to the list of immune-related adverse events associated with anti-PD-1 treatment for malignancies. This new form of anti-PD-1–related diabetes should be suspected from modification of body appearance with unusual fat loss, which should lead to further metabolic investigations.

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