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Case Report

Partial Lipodystrophy Affecting the Extremities in a Young Woman With Autoimmune Polyglandular Syndrome 1

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Abstract

Autoimmune polyglandular syndrome 1 (APS1) is an autosomal recessive disorder due to biallelic pathogenic variants in the autoimmune regulator (*AIRE*) gene that manifests with chronic mucocutaneous candidiasis, primary hypoparathyroidism, and adrenal insufficiency. We report a 39-year-old woman with APS1 who developed partial lipodystrophy during adulthood. She presented with diaper rashes, oral thrush, and tetany during infancy due to candidiasis and hypoparathyroidism. During childhood, she developed hypothyroidism, primary adrenal insufficiency, and ovarian insufficiency.

At age 14, she received a sibling-matched allogenic bone marrow transplant due to multiple antibiotic-refractory fungal infections. At age 35, her serum triglycerides were 914 mg/dL (10.32 mmol/L) and she had loss of subcutaneous fat from the upper and lower extremities and hips. A whole-body dual-energy x-ray absorptiometry revealed lower-extremity fat at less than the first percentile. Whole-exome sequencing on DNA extracted from saliva revealed pathogenic variants, p.Leu28Pro and p.Arg257* in *AIRE* but none in the known lipodystrophy genes. Phage-immunoprecipitation-sequencing revealed the presence of autoantibodies to MAGEB1, MAGEB4, and RFX6, which have been previously reported in APS1. Our case suggests that patients with APS1 may develop partial lipodystrophy due to autoantibodies against novel adipocyte-expressed proteins. A causal relationship of high levels of autoantibodies in our patient to adipose tissue–expressed ODC1, NUCKS1, or FNBP1L and lipodystrophy remains uncertain.

Key Words: autoimmune polyglandular syndrome 1, partial lipodystrophy, PhIP-Seq, AIRE

Abbreviations: *AIRE* gene, autoimmune regulator; APS1, autoimmune polyglandular syndrome 1; GVHD, graft-versus-host disease; mTECs, medullary thymic epithelial cells; PhIP-Seq, phage immunoprecipitation sequencing; PLIN1, perilipin-1; WES, whole-exome sequencing.

Introduction

Autoimmune polyglandular syndrome 1 (APS1) is a rare autosomal recessive disorder that classically manifests with chronic mucocutaneous candidiasis, primary hypoparathyroidism, and primary adrenal insufficiency [1]. It is caused by biallelic pathogenic variants in the autoimmune regulator (*AIRE*) gene. Manifestations occur as early as age 5 years. Autoimmunity develops due to the escape of autoimmune T cells from the thymus, and many other autoimmune diseases, such as autoimmune thyroiditis, gonadal insufficiency, type 1 diabetes mellitus, pernicious anemia, intestinal malabsorption, autoimmune hepatitis, vitiligo, alopecia, ectodermal dysplasia, enamel hypoplasia, keratoconjunctivitis, and periodic fever, have been previously reported in APS1. Lipodystrophy as an associated illness in APS1 has been reported previously in only one patient [2]. We present another case of APS1 in a patient who developed partial lipodystrophy in early adulthood.

Case Presentation

The protocol was approved by the institutional review board of UT Southwestern, Dallas, Texas, USA. The patient provided written informed consent.

A 39-year-old woman of European ancestry developed frequent diaper rashes, oral thrush, and tetany at age 1 year. She was diagnosed with chronic mucocutaneous candidiasis and hypoparathyroidism, and oral calcium and magnesium supplementation was begun. At age 3 years, she developed bilateral keratitis from alacrimia and was treated with cyclosporine eye drops. As a toddler, she required dental crown restoration due to enamel hypoplasia. Due to short stature, she received growth hormone supplementation from age 5 to 15 years. At age 6, she developed hypothyroidism and received levothyroxine until age 15.

She was diagnosed with asthma at age 9 years and had recurrent episodes of bronchitis and pneumonia, some warranting

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hospitalization. At age 11, she developed primary adrenal insufficiency with the initiation of fludrocortisone and hydrocortisone. She had vitiligo and achromotrichia of the eyelashes and scalp hair at age 10. At age 11, she had serial fungal otitis externa and candida esophagitis treated with antifungals, which were continued prophylactically until age 16. She also had autoimmune hepatitis at age 12, requiring brief treatment with 6-mercaptopurine.

At age 13, she developed pubic hair and breasts but never attained menarche. At age 14, she underwent a sibling-matched allogenic bone marrow transplant due to multiple refractory fungal infections. She was conditioned with 9 treatments of total body irradiation for a total dose of 1350 Gy and intravenous cyclophosphamide 2360 mg/day for 2 days (total of 4720 mg). She received methotrexate and cyclosporine for graft-versus-host disease (GVHD) prophylaxis. After the transplant, her dentition and liver function tests improved, vitiligo progression was arrested, and she did not require levothyroxine; however, her pubertal growth arrested.

A year after the transplant, she developed a large pericardial effusion that required surgical drainage at age 15. At age 16, she developed GVHD presenting as bronchiolitis obliterans, which was treated with pulse steroids followed by high-dose prednisone for 6 months. Subsequently, she was diagnosed with primary hypogonadism and started on oral estrogen and progesterone replacement therapy. Sex steroid therapy was discontinued after the development of a venous thrombus at age 27.

At age 31, her total cholesterol was 243 mg/dL (6.28 mmol/L); low-density lipoprotein cholesterol, 141 mg/dL (3.65 mmol/L); high-density lipoprotein cholesterol, 63 mg/dL (1.63 mmol/L); and triglycerides, 194 mg/dL (2.19 mmol/L). An antinuclear antibody, anti-isthmus, and anti-islet cell antibody screen were negative. At age 32, she was diagnosed with a right atrial myxoma requiring catheter-mediated removal. At age 34, she developed idiopathic seizures, restrictive lung disease, and had a hysterectomy and bilateral salpingo-oophorectomy for uterine leiomyomata and adenomyosis.

At age 34, she had minimal subcutaneous fat on her arms, legs, and hips but was noted to have increased subcutaneous fat in the chest, abdomen, and dorsocervical region (Fig. 1). Skinfold thickness measurements were below the tenth percentile at the thigh but were above the median or more than the 90th percentile at the truncal skinfolds (axilla, chest, subscapular, abdomen, and suprailiac sites) (Fig. 2). A whole-body dual-energy x-ray absorptiometry scan revealed a total body fat of 38% with 27% fat in the left leg (T- and Z-score of −2.2) and 25.5% in the right leg (T- and Z-score of −2.5). The T and Z scores for the left arm, right arm, and trunk were between 0 and 1.1. A diagnosis of autoimmune partial lipodystrophy was made.

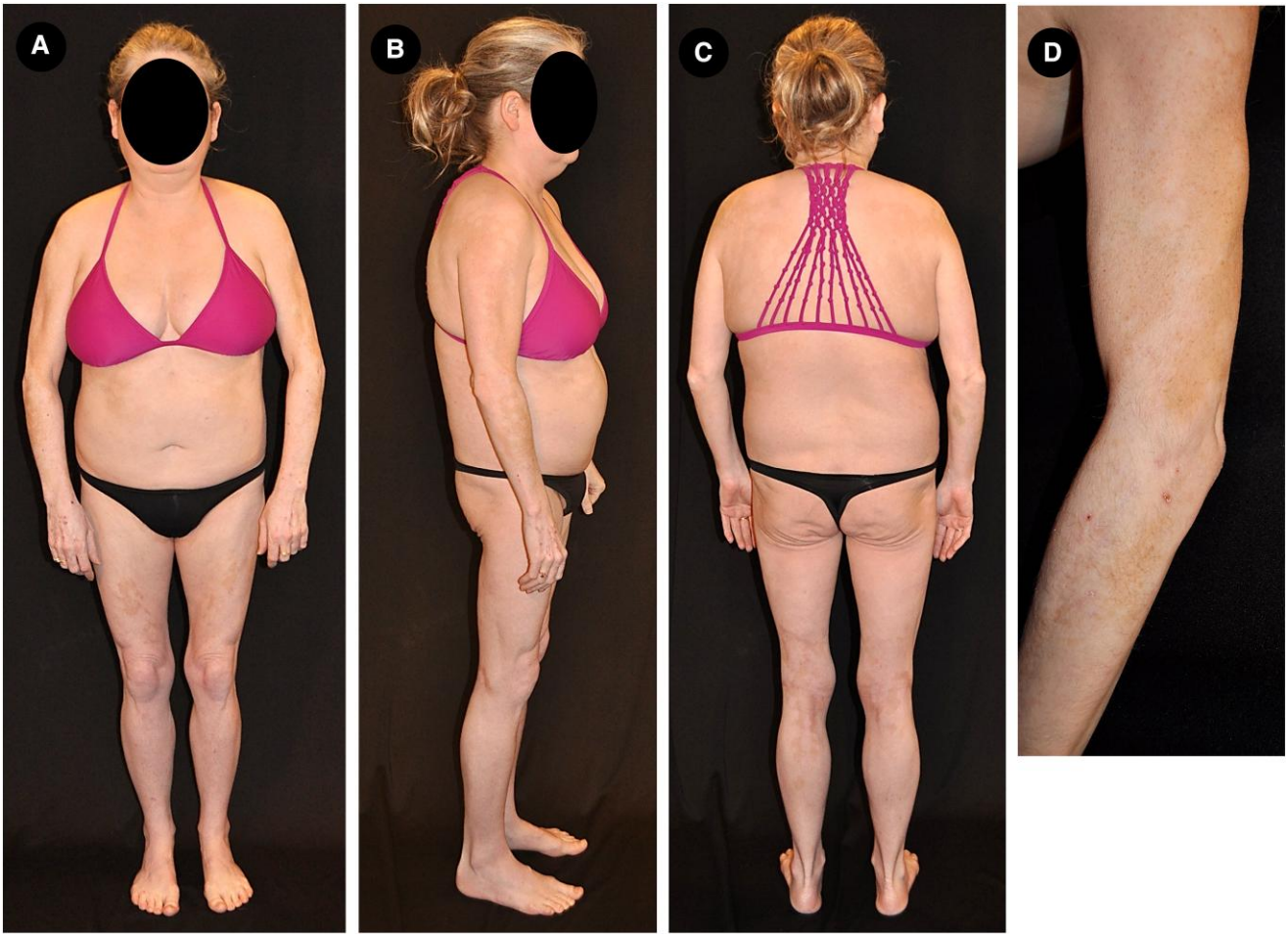

Figure 1. Clinical features of the patient. A, Anterior; B, right lateral; and C, posterior views of the patient at age 34 years showing scarce subcutaneous fat in the arms, forearms, gluteal region, thighs, and calves with prominence of underlying muscles. She had increased subcutaneous fat in the face, chin region (double-chin), chest, and abdomen (protuberant abdomen). D, Lateral view of left upper extremity showing patches of vitiligo and loss of subcutaneous fat.

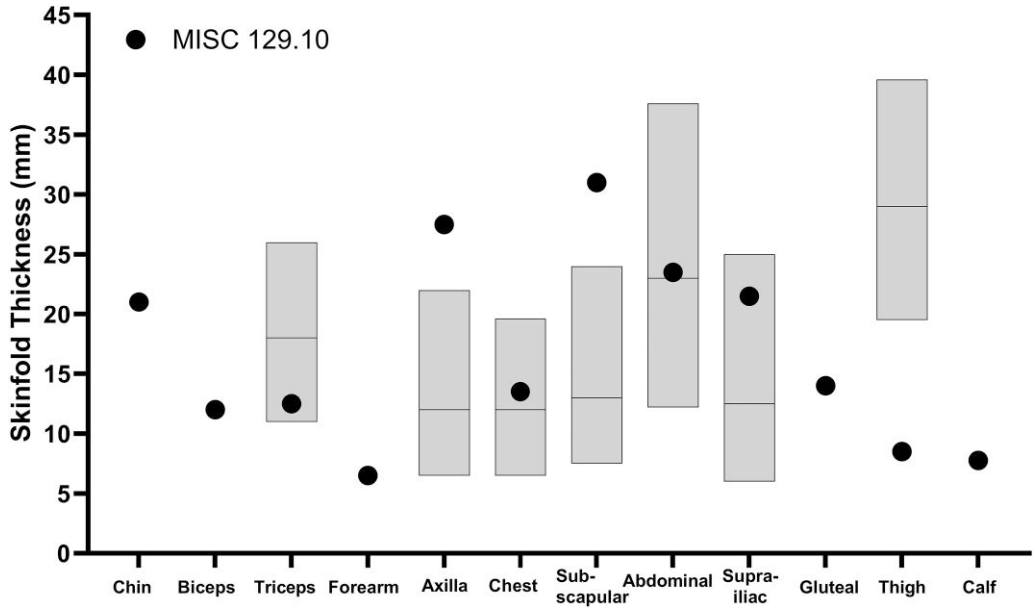

Figure 2. Skinfold thickness of the patient at various anatomical sites compared to normal data. Skinfold thickness data of the patient at age 34 years are shown as black circles. The gray vertical bars indicate 10th to 90th percentile values of normal women with median value as horizontal line in between the bars [3].

At age 35, she underwent a right-lung upper-lobe wedge resection, which revealed abundant nonnecrotizing granulomas requiring high-dose prednisone for several months. Her lipid panel deteriorated with a total cholesterol of 335 mg/dL (8.66 mmol/L), triglyceride level of 914 mg/dL (10.32 mmol/L), and high-density lipoprotein cholesterol of 46 mg/dL (1.19 mmol/L). Serum complement 4 level was 34 mg/dL (0.34 g/L) (normal range, 15-57 mg/dL) and complement 3 level was 186 mg/dL (1.86 g/L) (normal range, 83-193 mg/dL).

Diagnostic Assessment

Whole-exome sequencing (WES) was conducted on DNA extracted from the buccal cells using the IDT xGen Exome capture kit and sequenced on an Illumina platform to search for pathogenic variants in *AIRE* and lipodystrophy candidate genes, including *AGPAT2*, *AKT2*, *BSCL2*, *CAV1*, *CIDEC*, *LIPE*, *LMNA*, *PCYT1A*, *PIK3R1*, *PLIN1*, *POLD1*, *PPARG*, *PSMB8*, *PTRF*, and *ZMPSTE24*.

Phage immunoprecipitation sequencing (PhIP-Seq) was used to identify the presence of autoantibodies in the serum as described previously [4]. All peptide counts mapping to the same antigen were summed for this analysis. A fold change over the mean of 60 healthy controls was then calculated.

The patient's serum was also tested for antiperilin-1 autoantibodies by radioligand binding assay as described previously [5].

Treatment

In addition to dietary modification, the patient was started on gemfibrozil therapy 600 mg twice a day by mouth and her lipid profile improved.

Outcome and Follow-up

The WES identified 2 pathogenic variants in *AIRE*, c.83T > C; (p.Leu28Pro), considered as pathogenic or likely pathogenic [6], and c.769C > T (p.Arg257*), which is pathogenic [7]. Given the patient's presentation, we tested her for the presence of antiperilipin 1 autoantibodies, which we have previously linked to acquired generalized lipodystrophy in a patient with APS1 [2]. The patient's serum was negative for antiperilipin 1 autoantibody by radioligand binding assay. Since the patient had a large number of autoimmune conditions due to APS1, we next turned to a broad assessment of her autoantibodies using proteome wide phage display (PhIP-Seq). PhIP-Seq identified 92 positive autoreactivities. The top 25 autoreactivities are shown in Fig. 3A. Out of these autoantigens, only NUCKS1, CYP7B1, ODC1, FNBP1L, B2M, SSR1, GFI1, GCNT4, and DCUN1D5 are expressed in the adipose tissue, with NUCKS1 and CYP7B1 showing medium expression and all others showing low expression (www.proteinatlas.org) (Fig. 3B). Of the previously known autoantigens in APS1, our patient showed reactivity only for MAGEB1 (59-fold), MAGEB4 (30-fold), and RFX6 (5-fold) compared to healthy people on PhIP-Seq.

Discussion

In the thymic medulla, medullary thymic epithelial cells (mTECs) present tissue-restricted antigens to immature T cells to test for affinity toward self-antigens to select and promote apoptosis in those T cells that bind strongly to self-antigens. Thus, they prevent the migration of such T cells into the blood and prevent autoimmunity. The AIRE protein is expressed by the mTECs and facilitates the expression of self-antigens by mTECs [8]. Biallelic pathogenic variants in *AIRE* hinder the aforementioned process leading to autoimmunity manifesting as APS1 [9]. Our patient carried 2 variants—p.R257*, the most frequent causal variant located in the SAND domain of AIRE, associated with high rates of candidiasis, and p.Leu28Pro, located in the CARD domain crucial for structural integrity and can inhibit nuclear localization and AIRE-mediated transcription [10]. Our patient had multiple

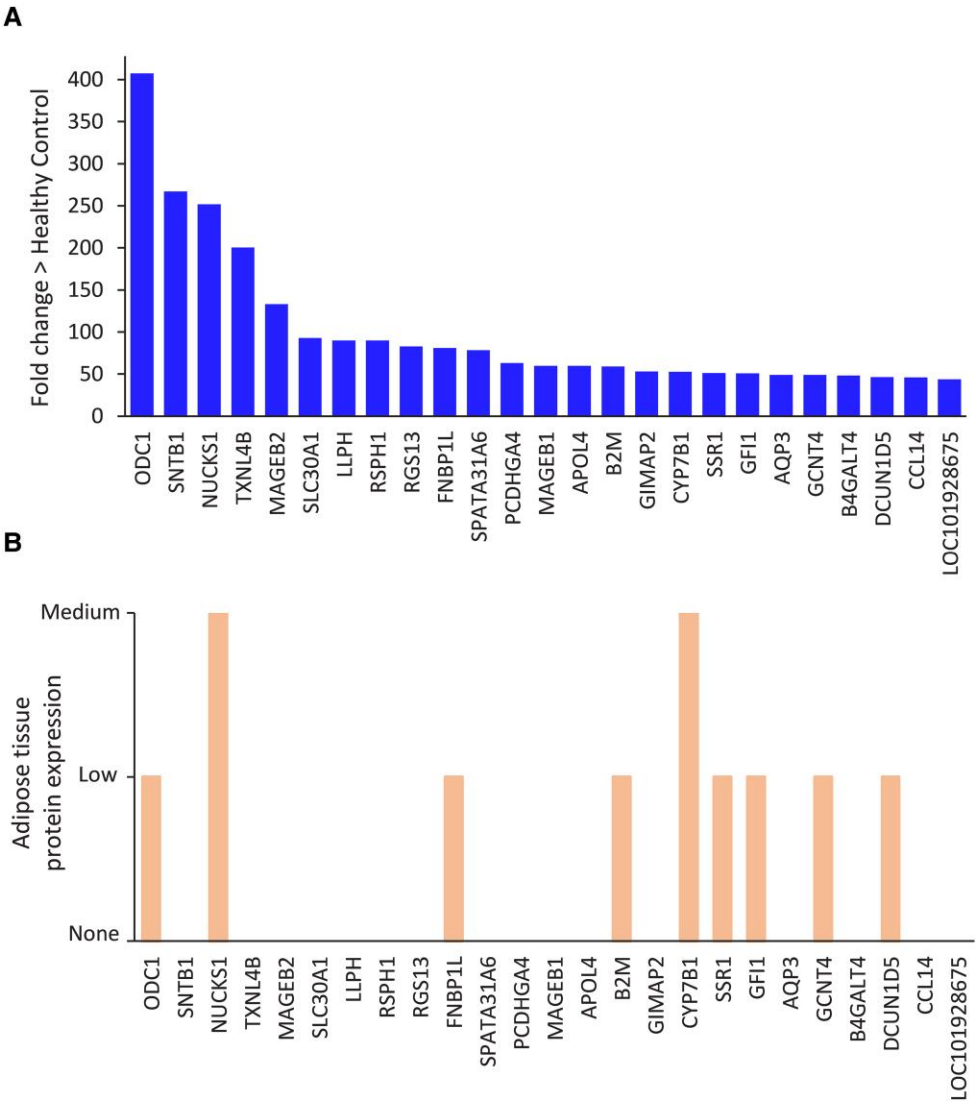

Figure 3. Autoreactivities in the patient's serum on phage immunoprecipitation sequencing (PhIP-Seq) and adipose tissue expression of identified autoantigens. A, The top 25 autoreactivities identified by PhIP-Seq in the patient are arranged in decreasing order with fold change over healthy controls depicted on y-axis. B, Adipose tissue expression of autoantigens showing top 25 autoreactivities in our patient (proteinatlas.org).

clinical manifestations at different time intervals throughout her life, which is characteristic of APS1.

Allogenic bone marrow transplantation carried out for other indications results in immunologic reconstitution in a few patients with chronic mucocutaneous candidiasis [11, 12]. Deeg et al [12] carried out the first such procedure in a 7-year-old girl with chronic mucocutaneous candidiasis and severe aplastic anemia from a human leukocyte antigen–identical sibling. The patient subsequently developed chronic GVHD but had resolution of chronic mucocutaneous candidiasis at 3 years' follow-up. Transplantation of AIRE overexpressing bone marrow–derived dendritic cells into mice with streptozotocin-induced type 1 diabetes mellitus delays the onset of diabetes mellitus, decreases the level of insulin autoantibodies, and better preserves islet structure [13]. Another X-linked recessive polyendocrinopathy, immune dysregulation and enteropathy (IPEX), has been treated with allogenic bone marrow transplantation [14]. To our knowledge, this is the first case of chronic mucocutaneous candidiasis due to APS1 where partial improvement in autoimmune conditions was observed with an allogenic bone marrow transplantation.

Our patient was diagnosed with partial lipodystrophy of the upper and lower extremities and buttocks into her adult life. There was sparing of the face, neck, and trunk in this case. Interestingly, most patients with classic acquired partial lipodystrophy (also known as Barraquer-Simons syndrome) lose fat in a cephalocaudal distribution affecting the face, neck, upper limbs, thorax, and abdomen, usually sparing the lower extremities [15]. The pattern of fat loss in our patient was unlike that seen in acquired partial lipodystrophy but was similar to that seen in patients with familial partial lipodystrophy. However, on WES no pathogenic variants were discovered in any gene associated with lipodystrophy.

Previously, only a 5-year-old boy with APS1 has been reported to develop acquired generalized lipodystrophy [2] and had circulating autoantibodies to perilipin-1 (PLIN1) [5]. PLIN1 is the most abundant protein in lipid droplets and it regulates lipid droplet size in adipocytes. PLIN1 autoantibodies were also reported in 37% of patients presenting with acquired generalized lipodystrophy [5]. Although our patient with APS1 did not have PLIN1 autoantibodies, it is most

likely due to the previous bone marrow transplantation. It is possible that the onset of lipodystrophy was prior to the bone marrow transplantation but was diagnosed later in adult life. If there were PLIN1 autoantibodies at the time of onset of lipodystrophy, we were unable to detect those after bone marrow transplantation. It is also possible that our patient may have another autoantibody against an adipocyte-expressed autoantigen that is responsible for development of partial lipodystrophy. For example, our patient's serum had high autoantibody levels against ODC1, NUCKS1, or FNBP1L, which are expressed in adipose tissue. However, unlike PLIN1, none of the 9 autoantigens (among the top 25 hits) with adipose tissue expression are encoded by known lipodystrophy genes. Therefore, no firm conclusions can be drawn about an autoantibody linked to partial lipodystrophy in our patient.

Interestingly, our patient's serum did not reveal high levels of autoantibodies to CYP11A1, SOX10, KHDC3L, and NLRP5, which are associated with adrenal insufficiency, vitiligo, ovarian insufficiency, and hypoparathyroidism, all the major autoimmune manifestations she had due to APS1. Previously, autoantibodies to MAGEB1 have been linked to vitamin B_{12} deficiency and Sjögren-like syndrome in patients with APS1, and to MAGEB4 to nail dystrophy and alopecia, and to RFX6 to autoimmune hepatitis or gastrointestinal manifestations [4]. Interestingly, our patient had only autoimmune hepatitis. MAGEB1, MAGEB2, and MAGEB4 are all highly expressed in the testis and ovary, and though previous studies [4] have not identified an association between these autoantibodies and premature ovarian insufficiency, a link may exist in our patient.

In conclusion, we report a rare patient with APS1 who had various manifestations of autoimmunity including a partial lipodystrophy phenotype.

Learning Points

- Lipodystrophy could have an early or adulthood onset in people with APS1.
- Bone marrow transplantation could lead to improvement of certain autoimmune conditions in people with APS1.
- In people with APS1 and lipodystrophy, there might exist autoantibodies to antigens other than PLIN1.

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Contributors

All authors made individual contributions to authorship. A.G.: diagnosis and management of the patient and manuscript writing and editing. S.A.: gathering data and manuscript writing and editing. C.X.: methodology. A.B.: methodology and manuscript editing. M.S.A.: methodology and manuscript editing. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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