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Case report

Early-onset Chronic Keratitis as the First Presenting Component of Autoimmune Polyendocrinopathy Syndrome Type 1 (APS-1): A Case Report and Review of the Literature

Şimşek et al. Autoimmune Polyendocrinopathy Syndrome Type 1 Presenting with Chronic Keratitis

Enver Şimşek[1], Tulay Simsek[2], Oguz Cilingir[3]
[1]Division of Pediatric Endocrinology, Department of Pediatrics, Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey
[2]Department of Ophthalmology, Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey
[3]Department of Medical Genetics, Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey

What is already known on this topic?
Autoimmune polyendocrinopathy syndrome type 1 (APS-1) is a rare autosomal recessive disease. APS-1 is characterized by the clinical triad of chronic mucocutaneous candidiasis, hypoparathyroidism, and primary adrenocortical insufficiency. It has been reported that the complete triad was present only in 50% of patients at the age of 20 years. When a rare or atypical component is the presenting feature of the syndrome and the diagnosis of APS-1 is made based on the classic triad, the diagnosis is usually delayed.

What this study adds?
Our case presented with chronic mucocutaneous candidiasis (CMC) and recurrent idiopathic keratitis. Pediatric ophthalmologists should consider APS-1 in the differential diagnosis of early-onset recurrent keratitis in children if it is associated on of the major triad of APS-1.

Abstract
Autoimmune polyendocrine syndrome type 1 (APS-1), also referred to as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is a rare monogenic autosomal recessive autoimmune disease. It is caused by mutations in the autoimmune regulator (*AIRE*) gene. APS-1 is diagnosed clinically by the presence of two of the three major components: chronic mucocutaneous candidiasis (CMC), hypoparathyroidism, and primary adrenocortical insufficiency. A 3.3-year-old girl was presented with a carpopedal spasm to the pediatric emergency clinic. She had a history of recurrent keratitis, and chronic candidiasis as urinary tract infections and oral thrashes. Hypoparathyroidism (HPT) was diagnosed based on low serum concentrations of calcium and parathyroid hormone and elevated serum concentrations of phosphate, and treatment with calcium and calcitriol supplementation was started. Genetic testing revealed homozygosity for nonsense c.769C>T (p.R257X) mutation in exon 6 in the *AIRE* gene which was reported previously. At the age of 5.6 years, she was presented with an adrenal crisis, and treatment with hydrocortisone and fludrocortisone was started. The reported case highlights that unexplained chronic keratitis in children may be the first and most severe component of this syndrome. The classic triad of APS-1 may also appear in the first decade of life.
Keywords: *AIRE*, mutation, APS1, keratopathy, children, hypoparathyroidism

Enver Şimşek MD, Division of Pediatric Endocrinology, Department of Pediatrics, Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey
+90 505 496 23 02
enversimsek06@hotmail.com
0000 0003 0120 9976
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Introduction

Autoimmune polyendocrinopathy syndrome type 1 (APS-1) is a rare autosomal recessive disease caused by mutations in the human autoimmune regulator (*AIRE*) gene located on chromosome 21q22.3(1,2). *AIRE* encodes a protein, AIRE, which acts as a regulator of the process of gene transcription and is essential for self-tolerance. AIRE deficiency leads to the escape and extra-thymic spreading of autoreactive T-cell clones: this creates the basis for the onset of the autoimmune attack against several tissue-specific self-antigens (1,2). Autoantibodies against type 1 interferons (IFN) (IFN-α and IFN-ω) are specific findings for APS-1 (3).

APS-1 is characterized by the clinical triad of chronic mucocutaneous candidiasis (CMC), hypoparathyroidism, and primary adrenocortical insufficiency (PAI). Other endocrine and non-endocrine components, such as type 1 diabetes mellitus, Hashimoto's thyroiditis, various ectodermal abnormalities (keratopathy, alopecia, vitiligo, chronic dermatitis, and dental enamel hypoplasia), pernicious anemia, chronic diarrhea, autoimmune hepatitis, cutaneous vasculitis, and primary gonadal failure may occur with a different prevalence (4). Clinically, APS-1 is diagnosed by the presence of two major components of the triad or only one if a sibling has already been diagnosed with APS-1 (4). CMC is the most common first clinical manifestation in APS-1 (5). The median age at diagnosis of CMC is usually < 5 years old (1.0–6,5 years) (6). Hypoparathyroidism and adrenal insufficiency follow CMC, respectively. When a rare or atypical component is the presenting feature of the syndrome, the diagnosis of APS-1 is often delayed.

The prevalence of APS-1 varies considerably from country to country. The highest prevalence is found among Persian Jews (1:9000) (7), Sardinians (1:14 000) (8), Finns (1:25 000) (9), and Norwegians (1:90 000) (10).

Here, we present a case of APS-1 in a Turkish girl who presented with CMC and recurrent keratitis in the first year of life, and the other major components also presented in the first decade of life.

Case Report

A 3.3-years-old girl of consanguineous Turkish parents of first-degree cousins was referred by a local outpatient clinic with carpopedal spasms and tetany. She had a history of chronic keratitis, recurrent oral trashes, onychomycoses, and recurrent vulvovaginal candidiasis since 14-months-old. Hospital record in ophthalmology department revealed that there was a round corneal epithelial erosion in the inferior temporal cornea in the left eye (Fig. 1A). She was commenced on moxifloxacin and lubricating eye drops, and ciprofloxacin ointment. The ulcerated area became epithelialized in 15 days and a slight corneal haze remained (Fig. 1B). The patient was admitted four or more times in a year with the same complaints. In each admission, a similar lesion was observed in the same focus on the cornea. Two years later from the

first admission, she presented with severe blepharospasm and photophobia. Ophthalmological examination revealed spontaneous corneal perforation on the old ulcerated region. The Seidel test was positive and the iris prolapsed into the perforated corneal region. A corneal haze due to recurrent keratitis was detected in the upper periphery of the cornea in the left eye (Fig. 1C). Iris adhesion was improved by a contact lens placement, and the pupil returned to its normal shape. Chronic keratitis was treated by combinations of local antibiotics and corticosteroids.

Her family history revealed that she had healthy parents and a little brother (Fig. 2), and no family history of chronic illness, including autoimmune diseases.

On physical examination, she was 99 cm tall (75th percentile) with a weight of 15 kg (50-75th percentile), and a body mass index (BMI) of 14.5 kg/m^2 (25th percentile). Chvostek and Trousseau's signs were positive. Initial biochemical tests revealed that serum concentration of total calcium concentration was 6.7 mg/dL (reference range [RR], 8.6-10.2); phosphate, 7.0 mg/dL (RR, 3.3-5.6); alkaline phosphatase, 45 U/L (RR, 82-325); intact parathyroid hormone, 5.0 pg/mL (RR, 10-65); 25-hydroxyvitamin D, 69 ng/mL (RR, 32-85). Based on the clinical and laboratory findings, she was diagnosed with hypoparathyroidism and commenced on oral elementary calcium (50 mg/kg three times daily) and calcitriol (oral, 0.25 μg twice daily).Her plasma calcium level increased to 8.1 mg/dL at the third day of treatment. Based on the presence of diagnostic dyad (CMC and hypoparathyroidism) and the coexistence of chronic keratitis, our presumptive diagnosis was APS-1. During the COVID-19 pandemic, she was lost from the follow-up for 2.5 years. The patient was admitted to our pediatric emergency clinic again with a high temperature, nausea, vomiting, and drowsiness at the age of 6.5 years. On physical examination, the skin was pale, mucous membranes dry, eyes sunken, skin turgor poor, and axillary temperature 38.7 °C. Vital signs and laboratory findings are shown in Table 1. Laboratory test results revealed hyponatremia (125 mEq/L), hypochloremia (84 mEq/L), hyperkalemia (7.2 mEq/L), metabolic acidosis (pH, 6.9 and HCO_3, 12 mEq/L), and hypoglycemia (38 mg/dL), low serum cortisol value (1.2 μg/dL) and elevated serum adrenocorticotropic hormone (ACTH) value (653 pg/mL). Based on the clinical and laboratory findings, she was diagnosed with an adrenal crisis. Unfortunately, renin activity was not measured during the adrenal crisis. Tests on organ-specific autoantigens associated with APS-1 were performed. Serum 21-hydroxylase antibody level was 3.9 U/mL (reference <1.0). Antithyroid (antithyroid peroxidase and antithyroglobulin), anti-islet cell, anti-insulin, anti-glutamic acid decarboxylase 65, antimitochondrial and anti-tissue transglutaminase antibodies were all negative. She was hospitalized for a couple of weeks for an adrenal crisis. Intravenous fluid and hydrocortisone replacement therapies were started. Three days later, she was followed up with maintenance doses of oral hydrocortisone (15 mg/m^2 three times daily), with dose adjustments according to concurrent illnesses and stresses, and mineralocorticoid (100 μg once daily). The patient showed weight gain and remained asymptomatic under replacement therapy with oral elemental calcium, calcitriol, hydrocortisone, and fludrocortisone. Since APS-1 patients can develop asplenia insidiously, the patient was vaccinated against encapsulated bacteria (pneumococcus, meningococcus, *Haemophilus influenza* type b), and annual influenza vaccination was recommended., One year after, there was a widespread vitiligo on her face (Fig. 3A) and patch-like hair loss on occipital scalp (Fig. 3B). Six months later, at the age of seven years, patch hair loss area was replaced by depigmented hairs (Fig. 3C).

The concomitant diagnosis of hypoparathyroidism and PAI with a history of oral and urinary candidiasis fulfilled the clinical diagnostic criteria for APS1. Mutation analysis by next-generation sequencing in the AIRE gene revealed a documented homozygous missense mutation: c.769C>T (p.R257X) in exon 6. In addition, her parents and brother were identified as heterozygous carriers of the same mutations (Fig. 2), which coincides with the autosomal recessive pattern.

Discussion

APS-1 is a rare autosomal recessive autoimmune disease that is caused by *AIRE* gene mutations. The classic clinical triad of APS-1 is CMC, HPT, and PAI. It has been reported that the complete triad was present only in 50% of patients at the age of 20 years (2,11). CMC, except in Persian Jews, is the most common and the first presenting component, typically developing in infancy or early childhood (11). However, in a study of 23 Persian Jews (12), only four patients presented with CMC. The median age of onset for CMC was 3 years (range 0.08–33 years). In the present case, CMC appeared at 14 months old as recurrent moniliasis and urinary tract candidial infections. Hypoparathyroidism usually occurs following CMC, usually appears after CMC with the peak incidence between the age of 2-11 years (6,11), and it is the most common endocrine component in APS-1 patients. PAI appears most commonly following CMC and HPT in the second or third decades (11,13). PAI is generally the second most common endocrinopathy in patients with APS-1 with the peak incidence around 12 years of age. The diagnosis of PAI is usually made when the patient presents with the symptoms and signs of adrenal crisis. If the diagnosis of APS-1 is made based on the classic triad, the diagnosis is usually delayed. Even if a component of the classical triad is accompanied by one of the other minor components (e.g., alopecia, vitiligo, nail dystrophy, dental enamel dysplasia, and keratopathy), investigating APS-1 may be the most accurate approach. Once the diagnosis is confirmed, life-long follow-up through a multidisciplinary team should be planned without delay. Close monitoring of calcium, calcitriol, glucocorticoid, and mineralocorticoid maintenance doses is essential to avoid life-threatening events (e.g., hypocalcemia or adrenal crises). In the present case, following CMC and keratitis, HPT was diagnosed at the age of 3.2 years. The coexistence of CMC and HPT suggested the presumptive diagnosis of APS-1.

The ocular manifestations of APS-1 include chronic persistent keratoconjunctivitis, dry eye, iridocyclitis, cataract, retinal detachment, and optic atrophy (14). Keratitis is the first manifestation in only 3–14% of APS-1 cases and the frequency varies between 25% and 50% (11,14). Chronic keratitis was reported as the first presenting sign before any evidence of systemic disease in three of 69 Finnish patients with APS-1, and 25% of cases had bilateral keratitis (15). The APS1- associated keratopathy has been pointed out as an essential feature of APS1 rather than as a secondary manifestation. Chronic keratitis is usually accompanied by severe photophobia, blepharospasm, conjunctival redness, and decreased visual acuity. Keratitis in APS-1 patients is characterized by recurrent attacks and leads to irreversible scarring, deep vascularization, and blindness (15). In the present case, keratitis was the second manifestation of the disease, following CMC. Alopecia, vitiligo, and nail dystrophy were also accompanying manifestations. Topical steroids and antibiotics were used for the treatment of keratitis. The presentation of our case suggests that pediatric ophthalmologists should consider APS-1 in the differential diagnosis of early-onset and recurrent keratitis in children.

Anti-interferon-α and anti-interferon-ω autoantibodies have high specificity for APS-1 (3, 10). Testing for anti-interferon antibodies upon clinical suspicion may be helpful for the diagnosis of APS1. In our case, we could not assay anti-interferon antibodies, because this test was not available in our hospital at the time of this study. The diagnosis was confirmed by sequencing of the *AIRE* gene mutation to differentiate APS-1 from APS-1-like conditions (e.g., APS-2 and X-linked immunoregulation, polyendocrinopathy, and enteropathy [IPEX]). APS-1 is a monogenic, autosomal recessive disease caused by a mutation in the *AIRE* gene. In our case, the molecular test identified a homozygous nonsense c.769C>T (p.R257X) mutation in the *AIRE* gene. To date, more than 140 different mutations in the *AIRE* gene have been reported worldwide (16). The c769C>T (p.Arg257stop) nonsense mutation is the most common variant with previously documented 125 cases or more so far (1,2,17,18,19). It is a frequent mutation in Finnish (1,2,18), Norwegian (5), Italian (19), Turkish (20), and Serbian patients (17). R257X in exon 6 changes an arginine codon to a stop codon at amino acid position 257, which encodes a truncated, nonfunctional protein of 256 amino acids. The second most frequent mutation is c.967_979del13 (p.C322del13) which is prevalent in patients in Norwegian, British, French, North American, and Indian patients (5,21,22). The other frequent mutation c.415C>T (p.139X) is prevalent in Sardinian patients (23). In contrast, p.V80G and p.X46L+59aa mutations were reported only from Indian patients (22). The other mutations have been reported as isolated cases. Heterozygous dominant-negative *AIRE* mutations in the plant homeodomain 1 (PHD1) domain have also been described in Iranian Jews (24,25). These dominant-negative mutations are associated with milder diseases.

APS-1 is characterized by high phenotypic heterogeneity, with wide variability in the number of clinical manifestations, there is often a delay in the diagnosis. PAI is usually presented by a life-threatening adrenal crisis. Therefore the early diagnosis of APS-1 is crucial, even in the absence of the main triad. APS-1 should be considered in children who have one of the major components of the classical triad of this disorder with coexistence as one of the minor manifestations. Our case presented with hypoparathyroidism to the pediatric endocrinology department, and she had a history of CMC and chronic keratitis. Our case suggests that early diagnosis of APS-1, close monitoring of children by pediatric endocrinologists, and periodic evaluation of biochemical and hormonal parameters are essential to prevent severe and life-threatening events (i.e. hypocalcemia or adrenal crisis). Patients and their parents should be informed regarding symptoms and sick day management of adrenal insufficiency and hypoparathyroidism.

Conclusions

In conclusion, the diagnosis of APS-1 is usually delayed due to wide variations in clinical presentations. Our case highlights that early diagnosis of APS-1 is essential to allow the prevention of severe and life-threatening events (e.g., hypocalcemia and adrenal crisis). The diagnosis of APS-1 should be considered in all patients presenting one of the major clinical manifestations coexistent with other minor manifestations of the disease. The diagnosis can be confirmed by sequencing the *AIRE* gene where available. Our case also highlights that recurrent keratitis in children may be an early and severe manifestation of APS-1.

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Disclosure and Conflict of Interest Statements

The authors have no financial disclosure and no conflict of interests to declare.

Parent consent

Written informed consent for publication of clinical details and images were obtained from parents.

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Table 1. Vital signs and laboratory findings at admission.

Clinical and laboratory findings (reference range)	
Vital signs	
Systolic BP, mmHg	85
Diastolic BP, mmHg	55
Heart rate, beats/min	112
Respiratory, rate/min	35
Laboratory	
Sodium, mEq/L (135-145)	125
Potassium, mEq/L (3.5-4.5)	7.2
Chloride, mEq/L (96-106)	84
HCO_3, mEq/L (22-26)	12
pH, (7.35-7.45)	6.9
Calcium, mEq/L (8.6-10.2)	7.1
Phosphorus, mEq/L (3.5-5.6)	6.9
Glucose, mg/dL (65-99)	38
Blood urea, mg/dL (5-18)	>100
Creatinine, mg/dL (0.5-1.2)	1.1
Hemoglobin, g/dL (13-16)	10.2
WBC, K/µL (4.8-13.1)	18.4
Neutrophil, % (33-77)	84
Lymphocyte, % (11-59)	10
Platelets, K/mL (189-394)	218
CRP, mg/L (0.0-5.0)	266
Procalcitonin, ng/mL (0.0-0.046)	2.25
Fibrinogen, mg/dL (170-420)	532
Cortisol, µg/dL (during hypoglycaemia; ≥ 20.0)	1.2
ACTH, pg/mL (8.5-65.5)	653
PTH, pg/mL (15-65)	4.7
25-OH Vitamin D, ng/mL (32-85)	19.8
FT4, ng/dL (0.96-1.77)	1.39
TSH, µIU/mL (0.7-5.97)	1.86
Urinary sodium, mEq/L (*)	111

Abbreviations; BP, blood pressure; WBC, white blood cells; CRP, c-reactive protein; ACTH, adrenocorticotropic hormone; PTH, parathyroid hormone; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TPO-Ab, thyroid peroxidase antibody; *, During hyponatremia high or low urine sodium concentrations (typically with 20 mEq/L as cutoff) can be used for differential diagnosis.

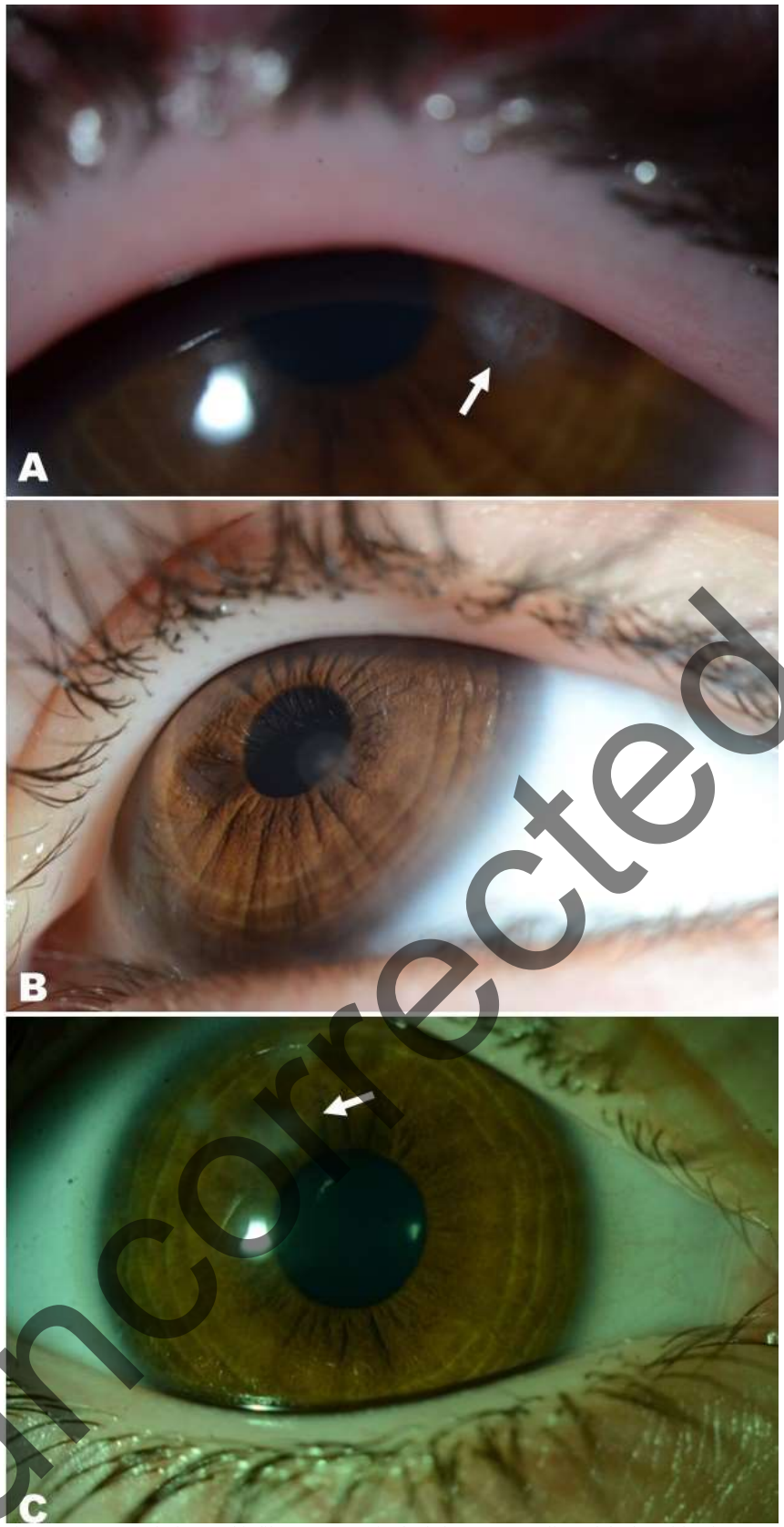

Figure 1. A, corneal ulcer and infiltrate (arrow) in the left eye; B, Healing of the keratitis after treatment; C, Haze in the peripheral cornea of the left eye (arrow) due to previous keratitis attacks.

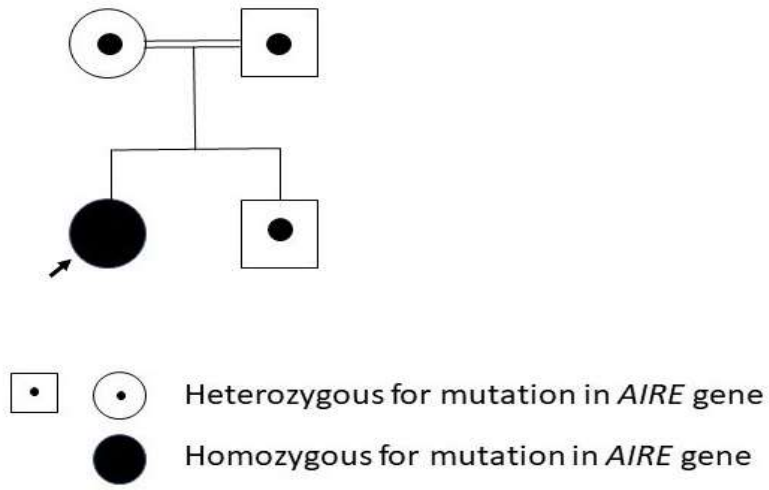

Figure 2. Family pedigree.

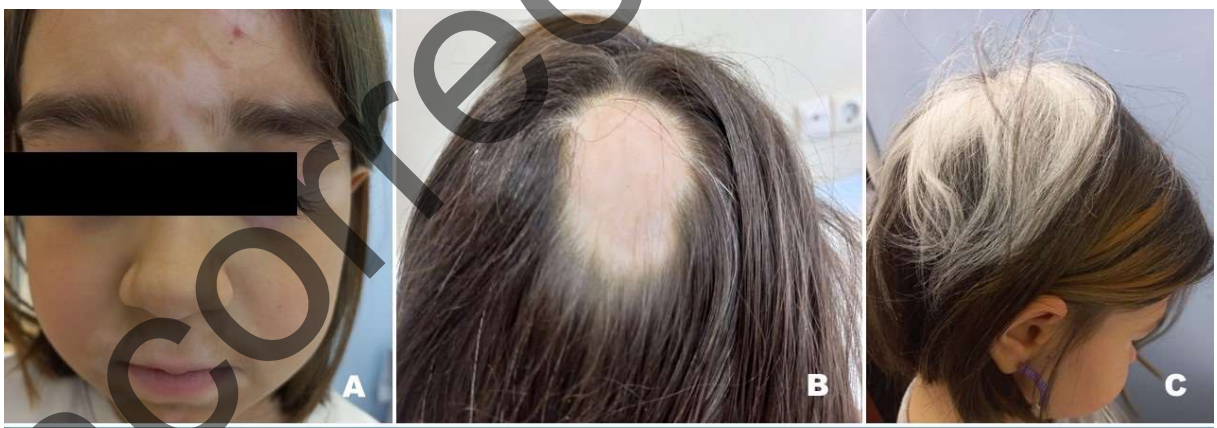

Figure 3. A, widespread vitiligo on her face; B, patch-like hair loss on occipital area; and C, patch-like hairy loss area was replaced by depigmented hairs.