Autoimmune Polyglandular Syndrome Type 2 (APS-2) is a rare condition with an incidence of 1–2/100 000 per year. Prevalence of APS-2 is most happening in the range of 20–40 years of age. Here we present a patient who complained about loss of appetite with significant weight loss also having trouble with her skin saying she had experienced progressively darkening of the skin all over her body and manifestations of Addison's disease at the age of 70. The patient was treated with oral Prednisolone, Fludrocortisone and Levothyroxine and evaluated after one month which showed the hormonal panel within the normal range.

Keywords: Autoimmune polyglandular syndrome, Addison's disease, Hypothyroidism, Schmidt Syndrome

Case Report

A 70-year-old East-Mediterranean woman presented with generalized fatigue that had been going on for two months and had been developing gradually. In addition she had trouble doing the daily chores. The patient had no medical history previously and did not take any drugs either. Patient also complained about loss of appetite and she had lost around 10 kg over the last year. Moreover she had been having trouble with her skin saying she had experienced progressively darkening of the skin all over her body and on her hands and her face to be precise, over the last 10 years. Patient had no history of smoking or usage of either opium or alcohol.
On physical examination, the patient was lethargic and had low blood pressure: 90/60 mmHg with orthostatic hypotension. Hyperpigmentation of the skin (Figures 1 and 2) and mucus membranes were seen (Figures 3 and 4). Thyroid was found smaller than the normal size while palpating. With the impression of thyroid and adrenal issues following laboratory investigations were made.

According to high levels of serum thyroid stimulating hormone (TSH) and low levels of T4, the patient was diagnosed with hypothyroidism (Table 1). Furthermore, low level of Na and high level of K in company with high level of ACTH and low level of Cortisol along with the skin and mucosal manifestations, led us to diagnosis of Primary Adrenal Insufficiency (Table 2).

Adrenal failure was managed with 7.5 mg oral Prednisolone daily and 0.1 mg oral Fludrocortisone daily. She was also treated with levothyroxine 0.1 mg daily as a Hormone replacement therapy due to hypothyroidism.

Further evaluations were made one month later in order to follow Na and K levels.

Since Tuberculosis (TB) is one of the most prevalent causes of adrenal insufficiency, the patient was addressed to take a chest X-ray to evaluate any pulmonary or cardiac problem, which showed no evidence of parenchymal diseases or consolidations in the lung and the heart had normal shape, size and position. More over PPD test was negative as well (Figure 5).

### Table 1. Laboratory findings

| Result                  | Unit | Normal range |
|-------------------------|------|--------------|
| Blood biochemistry:     |      |              |
| FBS                     | 93   | mg/dl        | 60-110             |
| Creatinine              | 1.16 | mg/dl        | 0.6-1.2            |
| ALT                     | 16   | U/L          | <31                |
| AST                     | 20   | U/L          | <31                |
| ALP                     | 250  | U/L          | 64-306             |
| Bili.T                  | 1.01 | mg/dl        | 0.1-1.2            |
| Bili.D                  | 0.17 | mg/dl        |                    |
| LDH                     | 337  | U/L          | 160-420            |
| Calcium                 | 8.9  | mg/dl        | 8.5-10.8           |
| CPK                     | 49   | U/L          | <110               |
| Amylase                 | 69   | U/L          | <90                |
| Na                      | 132.8| mEq/L        |                    |
| K                       | 6.97 | mEq/L        |                    |
| Hormones                |      |              |
| TSH-ECL                 | 13.9 | μU/mL        | 0.27-4.2           |
| Thyroxin total (T-4)-ECL| 76.1 | nmol/L       | 66-181             |
| OH VitD-25              | 3.90 | ng/mL        |                    |
| A.C.T.H                 | >1250| pg/mL        | 0.1-46             |
| Cortisol-ECL (AM)       | 4.28 | mg/dL        | 5-25               |

Immunology
|                      | Result | Unit       | Normal range |
|----------------------|--------|------------|--------------|
| Anti TPO-IgG         | 38.5   | IU/mL      | Up to 35     |
| C.B.C                |        |            |              |
| W.B.C                | 6.3    | X10^3/μL   |              |
| R.B.C                | 4.92   | X10^6/μL   |              |
| H.B                  | 15.3   | gr/dL      | 12-16        |
| H.C.T                | 44.8   | %          |              |
| PLT                  | 172    | X10^3/μL   | 150-450      |

Urinanalysis

|                      |         |            |              |
|----------------------|---------|------------|--------------|
| Color                | Yellow  |            |              |
| Blood                | Negative|            |              |
| Protein              | Negative|            |              |
| Glucose              | Negative|            |              |
| Ketone               | Negative|            |              |
| W.B.C                | 3-4     | /hpf       |              |
| R.B.C                | 0-1     | /hpf       |              |

Figure 1&2. Darkening of the skin and hyperpigmentations on hands
Autoimmune Polyglandular Syndrome Type 2

Figure 3 & 4. Hyperpigmentations on the face and around teeth and mucus membranes

Table 2. Following up Na and K

| Blood Biochemistry:                      | Result | Unit  | Reference range |
|-----------------------------------------|--------|-------|-----------------|
| Sodium (NA)-ISE                         | 140    | mEq/l | 135-148         |
| Potassium (K)-ISE                       | 4.6    | mEq/L | 3.5-5           |
| 25-OH Vit D3                            | 18.1   | ng/mL | 30-150          |

Discussion

The term APS-2 is defined when an individual has at least 2 out of 3 of the following manifestations: Addison’s disease, autoimmune thyroid disease and type 1 diabetes mellitus. APS-2 is a rare condition; with an incidence of 1–2/100,000 per year. The female-to-male ratio of APS2 is 3–4:1 (5,6). APS2 is a condition that generally presents in the third and fourth decades of life (3,7). Our patient's presentation with adrenal insufficiency at the age of 70 was thus unusual and it is probable that her adrenal autoimmunity had been present for a remarkable time prior to development of clinical manifestation and diagnosis as it was mentioned by the patient that the symptoms began to appear gradually from 10 years ago. It is worth mentioning that the clinical features of Addison's disease do not begin to appear until at least 90% of the glandular tissue has been destroyed.

Different literatures found different data on coexistence of the three main diseases. However, coexistence of T1DM and thyroid disease was most common while the coexistence of Addison’s and thyroid disease was less common (8).
There were no symptoms or signs of other endocrine and non-endocrine manifestations of APS-2, like celiac disease, alopecia, vitiligo, primary hypogonadism, myasthenia gravis, IgA deficiency, pernicious anemia, idiopathic heart block, Stiff-man syndrome, Parkinson’s disease, serositis, dermatitis herpetiformis, idiopathic thrombocytopenia, and hypophysitis in our patient (3).

Although etiology of APS-2 is still under further evaluations, as far as known, it is a polygenic disease, with significant heterogeneity due to multiple genetic loci and environmental factors. Genetic studies revealed histocompatibility complex (MHC) genes located on chromosome 6 are involved in organ-specific damage. It appears that the syndrome is more prevalent in patients associated with specific HLA-DR3 and HLA-DR4 haplotypes and the class 2 HLA alleles DQ2 and DQ8; Non-HLA genes including CD25-interleukin-2 receptor, cytotoxic T-lymphocyte protein 4 (CTLA-4), and protein tyrosine-protein phosphatase, non-receptor type 22 (PTPN22) can also increase predisposition to APS-2 (1,9,10). Unfortunately nor genetic study neither the level of 21-hydroxylase antibody in our patient.

Conclusion

Patients affected with APS-2 may experience multiple challenges and also carry a significant burden due to the complexity of the disease. When there is an involvement of a single endocrine gland there can be possibility of involvement of a second gland at later date. In patients like ours which are having mild elevation of TSH with borderline levels of T4 which is accounted as subclinical hypothyroidism, not only should it be neglected by the patient, but also it should rise the suspicious for polyglandular syndromes, thus evaluating them clinically should be taken under consideration. Consequently specific tests should be performed if additional immune diseases are suspected.

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Conflict of Interest

Authors declared no conflict of interests.

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