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Autoimmune polyendocrine syndrome type 2 in patient with severe allergic asthma treated with omalizumab

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ABSTRACT

Asthma therapy with monoclonal antibodies is a promising and effective approach for those with a severe and refractory type of disease. Although such a targeted therapy is considered to be safe, unusual complications may occur. We present a case of a 45 year-old female patient with severe allergic asthma and chronic spontaneous urticaria, who developed autoimmune polyendocrine syndrome type 2 (APS-2) after 26 months of omalizumab administration. The patient was diagnosed with primary adrenal insufficiency (Addison's disease) and Hashimoto's thyroiditis accompanied by autoimmune atrophic gastritis. According to our knowledge this is the first description of APS-2 that developed in conjunction with omalizumab treatment, although we have no evidence that the observed phenomenon indicated a cause-effect relationship to omalizumab.

ARTICLE HISTORY

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Autoimmune polyendocrine syndrome type 2; omalizumab; asthma

Dear Editor,

In the June issue of the Journal of Asthma, Albers et al. (1) have demonstrated that therapy of asthma with monoclonal antibodies is a promising and effective approach for those with a severe, refractory type of disease. Although, such a targeted therapy is considered to be safe, unusual complications may occur. We present a case of a 45-year-old female patient with severe allergic asthma, epilepsy, and chronic spontaneous urticaria, who developed an autoimmune polyglandular syndrome type 2 (APS-2) after 26 months of omalizumab administration.

Case report

A 45-year-old female with chronic urticaria, epilepsy, long-standing history of severe allergic asthma, treated with omalizumab for 26 months, was admitted urgently to the Department of Allergy and Immunology in Krakow, Poland with complaints of abdominal pain, vomiting, joint pain, and weakness. Her symptoms had intensified over the last 4 weeks and were accompanied with diarrhea and unintended weight loss of 4 kg. On admission she was afebrile with sinus tachycardia (100/minute), hypotension (80/50 mmHg), and tachypnoe (20/minute). There were no skin lesions, but hyperpigmentation over the face and limbs was noticed. Physical examination revealed tenderness in the left upper quadrant of the

abdomen and middle epigastrium. Initial laboratory tests revealed mild leucopenia (3920/ μ l), hypoglycemia (3.5 mmol/l), and signs of impaired kidney function (estimated glomerular filtration rate by MDRD equation-26 ml/minute/1.73 m²). Potassium level was in the upper limit of normal values (5.0 mmol/l), while sodium and magnesium concentration fell below the reference range (134.0 mmol/l and 46 mmol/l, respectively). Serum, liver, and pancreatic enzymes, as well as inflammatory markers were within normal limits. Blood and urine cultures were negative.

Viral panels including human immunodeficiency virus, cytomegalovirus, Epstein-Barr, hepatitis B, and C virus were also negative. Chest X-ray, abdominal ultrasonography, and echocardiography did not reveal any pathology. The patient was treated with intravenous fluids and proton pump inhibitor with clinical improvement and normalization of the renal function. In the past 4 years she received prolonged systemic glucocorticoids due to severe asthma (methylprednisolone 6–8 mg per day). Oral glucocorticoids had been withdrawn 12 months earlier, thus we decided to check for a possible iatrogenic adrenal insufficiency. The morning cortisol was undetectable (<0.5 μ g/dl) with surprisingly elevated adrenocorticotropine hormone (ACTH) level of 997 pg/ml (normal range: 6–56). These results together with clinical symptoms met the

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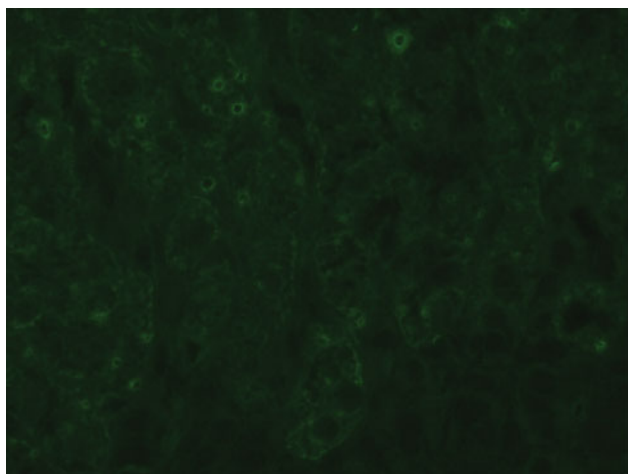


Figure 1. Antibodies against adrenal cortex cell (original magnification 400 $\times$). Monkey's adrenal cortex, indirect immunofluorescence 288 $\times$ 216 mm (72 $\times$ 72 DPI).

criteria for primary adrenal insufficiency according to the Endocrine Society (2). Further laboratory tests revealed the presence of antibodies against adrenal cortex cell, shown by indirect immunofluorescence (Figure 1) and steroid 21-hydroxylase autoantibodies in an ELISA (28.4, normal range: 0–10 IU/ml). These investigations indicated primary adrenal insufficiency (Addison's disease). Moreover, the thyroid-stimulating hormone was slightly elevated (6.95 μ IU/ml; reference range: 0.27–4.2) with a normal level of free thyroid hormones and highly positive anti-thyroid antibodies (anti-thyroid peroxidase antibodies 474.1; reference range: <34.0 IU/ml, and anti-thyroglobulin antibodies 311.8; reference range: <115 IU/ml), with a typical ultrasonographic pattern of Hashimoto thyroiditis. Laboratory tests also revealed

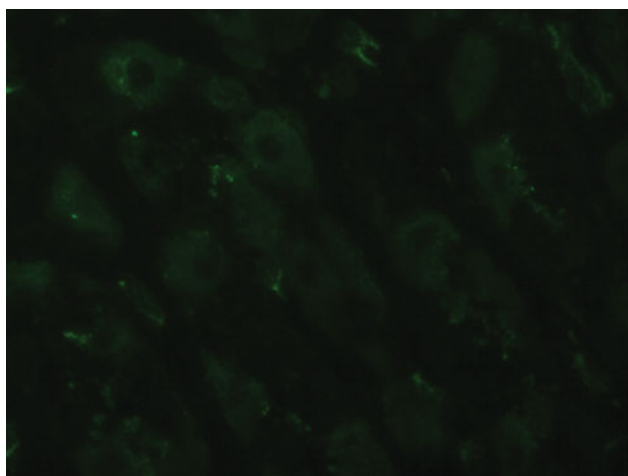


Figure 2. Antiparietal cell antibodies (original magnification 400 $\times$). Monkey's stomach, indirect immunofluorescence 288 $\times$ 216 mm (72 $\times$ 72 DPI).

the presence of intrinsic factor and parietal cell autoantibodies (Figure 2); vitamin B12 was within the normal range.

The patient was diagnosed with primary adrenal insufficiency (Addison's disease) and Hashimoto's thyroiditis accompanied by an autoimmune metaplastic atrophic gastritis (as confirmed in gastroduodenoscopy). She was started with hydrocortisone, followed by L-thyroxin therapy with clinical and laboratory improvement. Moreover, because we were not able to exclude a cause–effect relationship of this syndrome to omalizumab, we decided to discontinue this medication despite good asthma control. Unfortunately, after omalizumab termination, asthma symptoms rapidly deteriorated. The first severe asthma exacerbation was observed three months later. Currently (one year after omalizumab termination), the patient is treated with hydrocortisone (substitution therapy due to adrenal insufficiency), but she also receives prolonged treatment with methylprednisolone (6 mg per day). Symptoms of urticaria were not observed after omalizumab termination.

Discussion

APS-2 or Schmidt's syndrome is a rare autoimmune disorder characterized by the occurrence of autoimmune Addison's disease in combination with thyroid autoimmune inflammation and/or type 1 diabetes mellitus (2). Other autoimmune pathologies in this syndrome might include primary hypogonadism, myasthenia gravis, celiac disease, and autoimmune gastritis detected in our patient (3). The exact etiology of APS-2 remains unknown, similar to other autoimmunologic disorders. Previous studies highlighted the role of selected HLA alleles determining tissue specific targeting, which with the loss of immune tolerance may lead to organ specific autoimmunity (3,4). Other genes and environmental factors may also be involved in the pathogenesis of these diseases (3).

In our patient APS-2 emerged during prolonged (26 months) treatment with omalizumab. Prior to omalizumab therapy laboratory tests revealed normal thyroid hormones, as well as negative results for anti-thyroid antibodies. Morning cortisol, ACTH, or anti-adrenal gland antibodies were not assessed, because the patient had no clinical symptoms of adrenal insufficiency.

In the available literature, we did not find any evidence of an association between omalizumab and the occurrence of this disorder. However, a temporary relationship of the symptoms onset cannot rule out a causal linkage. It has been shown that omalizumab may improve interferon alpha (IFN- α) responses to rhinovirus and greater IFN- α increases were associated with fewer asthma

exacerbations (5). On the other hand, IFN- α therapy has been associated with a variety of autoimmune phenomena and increased risk of thyroid dysfunction (5). Krysiak et al. described a case in which APS-2 was induced by IFN- α treatment (6). According to our knowledge this is a first description of APS-2, which developed in conjunction with omalizumab, although we have no evidence that the observed phenomenon indicates a cause-effect relationship to this treatment. Moreover, in parallel with omalizumab, the patient received other medications, including montelukast, antihistamines, and primidone for epilepsy, which might be also related to the observed autoimmunity, similarly to the previously used oral glucocorticosteroids. Finally, we may speculate that APS-2 in this case developed as a co-morbidity and was not related to any biological or non-biological therapy.

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