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Macro-amylasemia in a patient with selective IgA deficiency and antiphospholipid antibodies

IgA eksikliği ve antifosfolipid antikorları olan bir hastada makro-amilazemi

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We report an unusual case with macro-amylasemia with coexistent selective IgA deficiency and antiphospholipid antibodies. A 16-year-old girl was referred to us with a history of episodic abdominal pain accompanied by vomiting and diarrhea. Macro-amylasemia was demonstrated by precipitation of 99% amylase activity with polyethylene glycol 6000. She had high levels of anticardiolipin IgG and β2 glycoprotein 1 IgG antibodies in the blood, but no evidence of clinical criteria of antiphospholipid syndrome. In the literature, although macro-amylasemia has been found to occur in a variety of diseases including autoimmune disorders, to our knowledge, this is the first well-documented case of macro-amylasemia associated with selective IgA deficiency and the presence of antiphospholipid antibodies. It is important that clinicians be aware of their existence in order to avoid unnecessary procedures and that the patient is informed of the macro-amylasemia; moreover, it should be stated in the patient's health record.

Key words: Macroenzymes, macro-amylasemia, IgA deficiency, autoimmunity, antiphospholipid antibodies

Selektif IgA eksikliği ve antifosfolipid antikorları ile birliktelik gösteren ilginç bir makroamilazemi vakası sunulmuştur. 16 yaşındaki bayan hasta, kusma ve ishalin eşlik ettiği epizodik abdominal ağrı hikayesi ile başvurdu. Makroamilazemi tanısı, PEG 6000 ile amilaz aktivitesinin %99 oranında çökertilmesi ile gösterildi. Hastada yüksek seviyelerde antikardiyolipin IgG ve β2 glikoprotein 1 IgG antikor pozitifliği mevcuttu, ancak antifosfolipid sendromu lehine klinik bir bulgu yoktu. Literatürde makroamilazemi, otoimmün bozuklukların da dahil olduğu bir çok hastalıkta bulunmasına rağmen, bildiğimiz kadarıyla, bu vaka selektif IgA eksikliği ve antifosfolipid antikor pozitifliği ile ilişkili olan dokümante edilmiş ilk makroamilazemi vakasıdır. Klinisyenlerin bu durumdan haberdar olmaları, gereksiz işlemlerden kaçınılması, hastanın makroamilazemi konusunda bilgilendirilmesi ve sağlık kayıtlarına işlenmesi açısından önemlidir.

Anahtar kelimeler: Makroenzimler, makroamilazemi, IgA eksikliği, otoimmünite, antifosfolipid antikorları

INTRODUCTION

Macroenzymes are complexes of serum enzymes, most commonly immunoglobulins, fewer proteins or lipoproteins that have a higher molecular weight and more prolonged serum half-life than found in unbound enzymes. Macro-amylase is the most commonly noted and first described macroenzyme in the clinical laboratory of healthy individuals (1-16). However, it has been reported in case reports in the literature that macro-amylasemia is found in a variety of disorders such as celiac disease, lymphoma, carcinoma, systemic lupus erythematosus (SLE), rheumatoid arthritis and liver disease (2, 3, 5-14). Macro-amylasemia together with IgA deficiency is rare and only one case has been reported in the literature to date (2). Herein, we report a patient who had macro-amylasemia associated with selective IgA deficiency and antiphospholipid antibodies.

CASE REPORT

A 16-year-old Caucasian girl was referred to us with the complaint of abdominal pain and hyperamylasemia. The pain was at the hypogastrium and accompanied by vomiting and diarrhea, which occurred five times a day. Her symptoms started one year ago and she had four episodes of pain attacks during the year. Each of the episodes lasted about two or three hours and was characterized as

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lasting intermittently all week and resolving after treatment with non-steroid analgesics. She had recurrent sino-pulmonary infection history. There was no personal or familial history of familial Mediterranean fever (FMF), inflammatory bowel disease, or autoimmune disease. The physical examination appeared normal except for livedo reticularis on the extremities. Routine complete blood count and C-reactive protein were normal, but erythrocyte sedimentation rate was 38 mm/hour. On the microbiological examinations of the feces, no pathogen bacteria or parasites were found. Total protein, albumin, bilirubin, lipid profile, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase, lactate dehydrogenase (LDH) and lipase were normal, but she was found to have a persistently increased amylase activity in serum biochemical analyses. Repeat serum amylases were 319 IU/ml and 369 IU/ml (normal, 10-90 IU/ml) with quantitative urine amylases of 15 U/hour and 10 U/hour (normal, 50-400 U/h). Pancreatic amylase was 163 IU/ml (normal, 13-53 IU/ml). The amylase-to-creatinine clearance ratio was 0.4% (normal, 1.8-3.2%). A diagnosis of macro-amylase was suspected. Polyethylene glycol 6000 precipitated 99.4% of the patient's serum amylase, consistent with macro-amylasemia (4). Her parents and brother had no hyperamylasemia. Her serum protein electrophoresis and thyroid function tests were normal. The patient had no MEFV gene mutations for FMF. Screening for autoantibodies including antinuclear antigen, rheumatoid factor, anti-extractable nuclear antigen, anti-smooth muscle, antiendomysial and antigliadin antibodies was negative, but anti-neutrophil cytoplasmic antigen (ANCA) was ++ positive. Antibodies' profile of ANCA by ELISA was anti-myeloperoxidase (MPO) of 25.8 U/ml (normal 0-15), anti-PR3 of 41.9 U/ml (0-15), anti-lactoferrin of 17.8 U/ml (normal 0-15), anti-elastase of 41.2 U/ml (normal 0-15), anti-cathepsin 24.1 U/ml (normal 0-15) and anti-BP of 40.3 U/ml (normal 0-15). The patient had no evidence of SLE or vasculitis. Lupus anticoagulant antibody was negative. Anti-β_2 glycoprotein 1 IgM, IgA and anticardiolipin IgM antibodies were normal, but anti-β_2 glycoprotein 1 IgG (267.1 U/ml, normal 0-7) and anticardiolipin IgG (278.3 U/ml, normal 0-48) antibodies were at high levels in blood on two occasions eight weeks apart. Factor V Leiden, prothrombin gene and methionine tetrahydrofolate reductase gene mutations were negative. The Doppler ultrasonographic examination of the bilateral low extremities, echocardiography and pulmonary computerized tomographic (CT) angiography to search thrombosis were normal. Serum immunoglobulin determination by nephelometric test revealed an IgA of 0.54 g/L (repeat value was 0.41; normal 0.7-4 g/L), but IgG and IgM levels were in the normal range. Complements (C) including C3, C4 and CH50 were also normal. Serological tests for hepatitis B and C virus, cytomegalovirus, mumps and rubella were all negative. CT examinations of the pancreas and lungs were normal. She underwent upper gastrointestinal endoscopy and a duodenal biopsy. Mucosal nodularity was observed in the duodenum on upper gastrointestinal endoscopy (Figure 1).

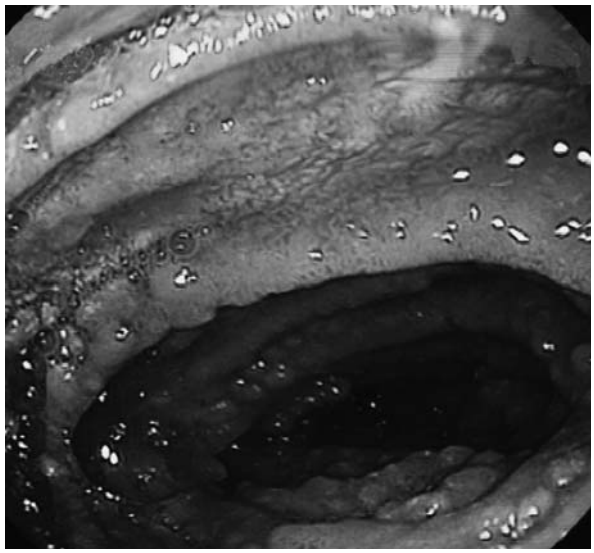

Figure 1. Mucosal nodularity was observed in the duodenum on upper gastrointestinal endoscopy

Biopsy revealed diffuse infiltration of the lamina propria predominantly by plasma cells with no obvious change in villous architecture or intraepithelial lymphocyte infiltration in the surface epithelium (Figure 2). Immunohistochemical analysis showed that plasma cells expressed both kappa and lambda light chains, hence demonstrating their polyclonal nature. Her recto-sigmoidoscopic examination was completely normal. A low-dose acetyl salicylic acid treatment was started because she had high levels of antiphospholipid antibodies. The diagnosis was documented in the patient's permanent medical record and she was followed for three months.

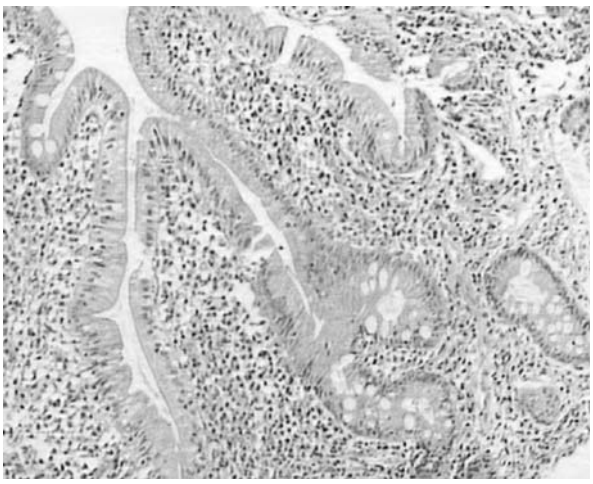

Figure 2. Diffuse plasma cell infiltration of the lamina propria (H&E; x200)

DISCUSSION

While elevated levels of serum enzymes are usually associated with a pathological condition, on rare occasions they may indicate the presence of a benign phenomenon known as a macroenzyme (1). Their existence was first reported by Remaley et al. (16), who described elevated levels of serum amylase and globulin. Since then, creatine kinase (CK), LDH, ALP, and AST were also reported to appear in a macroenzyme form. For the most part, macroenzymes are composed of an enzyme immunoglobulin complex; however, other forms of macromolecules (containing enzyme and lipoprotein or enzyme oligomers) have been observed as well. The most common macroenzymes are macro-amylase and macro-CK. A failure to detect a macroenzyme as the cause of an unexplained increase in enzyme levels can result in performance of expensive, unnecessary and often invasive procedures in search of an alternative diagnosis. The prevalence of macro-amylasemia in the general population is 1%, but patients with increased amylase are frequently overlooked (1, 6, 16).

The pathogenesis of macroenzyme formation is unknown. However, classic immunologic models of autoantibody formation have been proposed as potential explanations. In the 'antigen-driven' theory, a self-antigen is altered or released from a sequestered site in the body and it cross-reacts with an antibody initially formed against a foreign antigen. A second theory is the 'dysregulation of immune tolerance', which is likely to occur in autoimmune disorders, though few reported patients with macro-amylase had evidence of other autoimmune diseases (1). Catassi et al. reported the case of a two-year-old girl with macro-amylasemia and selective IgA deficiency (2).

Our case had intermittent abdominal pain, livedo reticularis, selective IgA deficiency and antiphospholipid antibodies (aCL-IgG and β_2 glycoprotein 1 IgG). The presence of abdominal pain in the patients with macro-amylasemia is not surprising, as this was the primary reason for measuring the amylase levels. This experience was previously implicated in the case reports of the patients with macro-amylasemia (2, 11). The diagnosis of antiphospholipid syndrome was not confirmed in our patient because she had no clinical criteria, including thrombosis and complication of pregnancy, although she had persistent high levels of antiphospholipid antibodies. Although the patient did not fulfill the revised criteria for the classification of antiphospholipid syndrome, we started aspirin as a prophylactic therapy because she supposedly had an increased risk of thrombosis (18).

Although coexistence of macro-amylasemia with some disorders has been reported in the literature, to our knowledge, the phenomenon of coexistence of macro-amylasemia with selective IgA deficiency and antiphospholipid antibodies as presented herein is the first well-documented case. An autoimmune disease and/or anti-phospholipid syndrome may develop in the long-term follow-up of the patient. For this reason, the patient and her family were informed of such an occurrence and she has been taken into a follow up.

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