

CA 125: Marker of serosal inflammation in hereditary angioedema?

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Key words: angioedema; CA 125.

Hereditary angioedema (HAE) is a rare autosomic dominant disease of variable penetrance without predominance in any racial group or sex. It manifests as acute attacks of cutaneous or laryngeal, genital or abdominal mucosal swelling secondary to deficit of the plasmatic protease C1 inhibitor (C1-INH) in heterozygote individuals due to lack of control in the complement system and increase in vascular leakage (1).

We present a 37-year-old woman diagnosed in her childhood of HAE with recurrent abdominal attacks. She has been on permanent prophylaxis with low doses of attenuated androgens (Danazol 100 mg) reducing the number and intensity of attacks. Recently the patient started with acute abdominal pain in the suprapubic area, hemorrhagic vaginal discharge and thigh skin edema with ill-defined margins. The attack persisted even after the self-administration of three nonconsecutive doses of purified C1-INH (Berinert®, Aventis Behring) and increase of her usual dose of Danazol to 200 mg bid. No clear trigger was identified. Therefore, we performed initially an abdominal and transvaginal ultrasound visualizing a small uterine fibroid and a well-positioned cap without any other finding. Later, an abdominal scan showed free peritoneal fluid and bowel distension. Seventy-two

CA 125 elevation during HAE abdominal attack.

hours later the scan was repeated with oral contrast for differential diagnostic means showing clear regression of the ascitis. In the analytic controls performed there were no significant findings in the hematology or biochemistry. Complement levels were similar to those previously. Only an elevation of the tumor marker CA 125 (372 U/ml) pointed out during the attack (Fig. 1).

We present a case of abdominal attack with serosal involvement in a patient diagnosed of HAE during which an elevation of serum CA 125 was observed. CA 125 is a non-specific tumoral marker used specially in ovarian cancer for monitoring the efficacy of therapy and for early detection of recurrence (2). But elevated serum CA 125 levels have been reported in the literature in multiple benign and malignant pathologies with serosal involvement (cirrhosis, tuberculous peritonitis, pancreatic cancer, heart failure, etc.) (3, 4). It has been even suggested as a highly sensitive marker to detect ascites in patients with liver cirrhosis (5) or to evaluate the efficacy of therapy in tuberculous peritonitis (6). In our case it seems to correlate with serosal inflammation and ascites resulting from

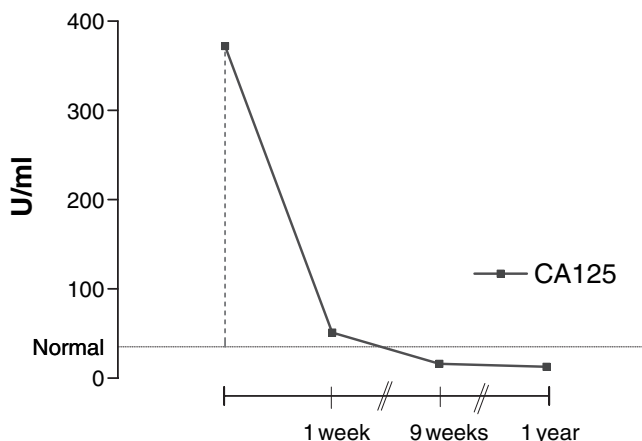


Figure 1. Serum levels of CA 125 during and after abdominal attack of hereditary angioedema.

extravasation into the peritoneal cavity. Interestingly, the levels of serum CA 125 normalized when the gastrointestinal wall edema had disappeared.

We describe the first case in literature of elevation of CA 125 during an abdominal attack of HAE. We suggest that serum CA 125 might be used as an early marker of serosal involvement and ascitis complementary to abdominal ultrasound for differential diagnostic purposes and to evaluate treatment response. Early recognition of acute abdominal attacks is of utmost importance because incorrect or delayed diagnosis often leads to unnecessary surgical intervention. Further confirmation of elevation of CA 125 during attacks is therefore necessary.

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The association of selective IgA deficiency and IgE hypogammaglobulinemia

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Key words: hypogammaglobulinemia; IgA; IgE; IgG subclasses.

Selective IgA deficiency has been associated with atopy and high serum IgE levels (1). Some small studies demonstrated its association also with low serum levels of IgE or IgE

hypogammaglobulinemia (2–7), which previously had been

noted to be associated with other primary immunodeficiencies such as common variable immunodeficiency and ataxia telangiectasia (8). The aim of the present study was to further explore combined IgA and

IgE deficiency in a larger cohort of patients with IgE hypogammaglobulinemia, and to describe its clinical presentation.

The database of the Clinical Immunology laboratory for 2001–2003 was searched to identify patients with serum IgE levels of < 10 IU/ml and serum IgA levels < 6.6 mg/dl, with normal IgG and IgM levels. For patients with combined deficiency, data were collected on age, gender, clinical diagnosis and serum IgG subclass levels. IgG subclass levels were compared with the normal range by age, as established in our laboratory. Levels below 2 standard deviations of the mean for age were considered low.

During 2001–2003, our laboratory performed 3287 tests for serum IgE, of which 532 (16.4%) yielded levels of < 10 IU/ml. Thirty-two of these patients had serum IgA levels of < 6.6 mg/dl. Seven of them had known primary immunodeficiencies (common variable immunodeficiency in five and X-linked agammaglobulinemia in two), and 19 were younger than 4 years, so that a diagnosis of selective IgA deficiency could not yet be made according to the criteria of the European Society for Immunodeficiency (9). The clinical features of the remaining six patients with selective IgA deficiency are presented in Table 1.

Table 2 summarizes the findings of previous studies of the association of selective IgA deficiency and IgE hypogammaglobulinemia. Our study included the largest number of patients with IgE hypogammaglobulinemia – 532 compared with 12 (6) and 44 (7) – most probably because of the large number of samples screened and our high cutoff of < 10 IU/ml relative to the 5 IU/ml (6) and 2.5 IU/ml (7) cutoffs in other studies. There is no established 'low level' for serum IgE, although Kjellman and Johansson found that serum IgE levels in healthy nonatopic children aged 0–14 years were > 5 IU/ml (10). Accordingly, three of six patients with concomitant selective IgA deficiency had serum IgE levels of 1–3 IU/ml, and in the other three patients, IgE levels were undetectable (Table 1).

The prevalence of selective IgA deficiency in our series of patients with IgE hypogammaglobulinemia was 1.12%,

lower than what was found in two previous studies of patients with IgE hypogammaglobulinemia (9–16.6%) (6, 7) (Table 2). In four other studies of patients with selective IgA deficiency, the prevalence of IgE hypogammaglobulinemia was 6.4–32% (2–5) (Table 2).

One possible explanation for the lower prevalence in our study is our exclusion of patients younger than 4 years, according to the criteria for selective IgA deficiency established by the European Society for Immunodeficiency (9), while other studies included also younger patients (Table 2).

Similar to previous studies, our patients with combined IgA–IgE deficiency had frequent upper and lower respiratory tract infections (patients 1, 4, 5 and 6) and bronchial asthma (patients 2 and 3). None had an autoimmune disease.

Two of our patients warrant special attention. Patient 4 had congenital heart disease and cleft palate, and cytogenetic analysis revealed a 22q11 deletion in 80% of the cells examined. The chromosome 22q11.2 deletion syndrome overlaps with DiGeorge syndrome (11), but the patient did not have any infection other than ear infections, and laboratory investigation did not reveal any evidence of cellular immune deficiency. Selective IgA deficiency has been described in patients with 22q11 deletion syndrome, but not in combination with IgG2, IgG4, and IgE deficiency (11).

Patient 6 had a more complicated course of pulmonary infections leading to bronchiectasis. His total serum IgG level was at the lower limit of normal. Further follow-up is needed to determine the future development of common variable immunodeficiency, as described previously in patients with selective IgA deficiency (12). Of the five patients with combined IgA–IgE deficiency who were tested for IgG subclass levels, four (80%) had concomitant IgG2–IgG4 subclass deficiency (Table 1). This finding is in accordance with previous studies wherein subclass deficiency rates in patients with IgA–IgE deficiency ranged from 15.3 to 50% (Table 2). In humans, the heavy chain for immunoglobulins is coded on chromosome 14 with IgA1, IgG2, IgG4, IgE and IgA2 in sequential order. Extensive multigene deletions have been

Selective IgA deficiency is present in 1.12% of 532 patients with IgE hypogammaglobulinemia.