

CASE REPORT

Development of Macro-Aspartate Aminotransferase in a Patient Undergoing Specific Allergen Injection Immunotherapy

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Macro-aspartate aminotransferase (macro-AST), a complex between normal AST and an immunoglobulin, is recognized as a cause of isolated elevation of AST. Though its pathogenesis is unknown, previous reports have been suggestive of an autoimmune process. We describe a case of macro-AST formation in a patient with previously normal liver enzymes in whom an isolated AST elevation was discovered after initiation of specific allergen injection immunotherapy (SIT) for allergic rhinitis. We propose that SIT in this otherwise healthy patient led to the formation of macro-AST as a consequence of antibody cross-reaction (molecular mimicry). Awareness of this possible mechanism of macroenzyme development may be helpful to physicians evaluating patients with isolated elevations in AST.

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INTRODUCTION

Macro-aspartate aminotransferase (macro-AST), one of the macroenzymes, is an increasingly recognized cause of isolated elevation of AST. It results from a complex between normal AST and an immunoglobulin (most commonly immunoglobulin G (IgG) or immunoglobulin A (IgA)) at the antigen-binding site of the immunoglobulin, leading to a high molecular weight form of AST (1, 2). This macroenzyme may elevate the total level of AST determined by routine serum chemistry as it is cleared more slowly than normal AST, perhaps through interference with reticuloendothelial system clearance mechanisms by the immunoglobulin–enzyme complex or through decreased renal filtration of the high molecular weight protein (3). The pathogenesis of macroenzyme formation remains undetermined, though an autoimmune process has been proposed as a potential mechanism. While it has been detected in diseases such as acute and chronic hepatitis, primary and metastatic hepatic malignancies, inflammatory bowel disease, and autoimmune disorders, macro-AST is most commonly found in an otherwise healthy patient (4–8).

Specific allergen injection immunotherapy (SIT) is an established treatment for allergy to insect venom and for allergic rhinitis, and has been studied in numerous other allergic conditions (9). In this report, we describe a patient with previously normal liver enzymes in whom an isolated elevation of AST developed after initiation of SIT, and who was subsequently determined to have macro-AST.

CASE REPORT

A 65-yr-old white male presented to our clinic in December 2003, for further evaluation of elevated AST and elevated an-

tismooth muscle antibody (ASMA) titer. He had had screening laboratory studies performed by an outside physician 2 months prior to presentation including a liver profile, which revealed an AST elevated at 132 U/L (normal 17–59 U/L) with normal range alanine aminotransferase, alkaline phosphatase, total bilirubin, gamma glutamyltransferase, and albumin.

Further evaluation by the patient's primary care physician included three additional liver profiles performed over the subsequent 2 months revealing persistent elevation of AST (43, 54, and 66 IU/L, normal <40 IU/L) with otherwise normal liver enzymes (Fig. 1). Antibodies to hepatitis C and hepatitis B surface antigen were nonreactive, and levels of creatine kinase, aldolase, antinuclear antibodies, and iron studies were all within normal limits. An ASMA titer was elevated at 1:160 (normal <1:20). Total cholesterol was 229 mg/dL (normal <200 mg/dL), triglycerides were 143 mg/dL (normal <150 mg/dL), low-density lipoprotein was 158 mg/dL (normal 30–130 mg/dL), and high-density lipoprotein was 42 mg/dL (normal 40–60 mg/dL). An abdominal ultrasound was performed and interpreted as having mild fatty infiltration of the liver with no other abnormalities identified. Notably, the patient provided laboratory reports of a liver profile performed 19 months prior to presentation that was completely normal.

The patient had no history of alcohol use, intravenous drug use, or high-risk sexual behavior. He had received multiple transfusions 13 years prior to presentation in the setting of a gastrointestinal bleed whose source was never identified. There was no personal or family history of liver disease, inflammatory bowel disease, or autoimmune disease. Past medical history was notable for allergic rhinitis but was

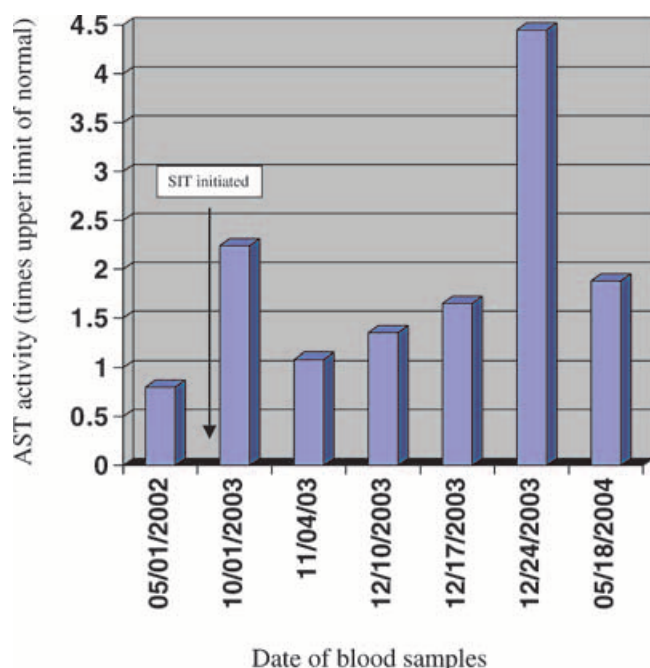


Figure 1. Changes in the patient's serum aspartate aminotransferase (AST) activity over a 2-year period. AST was normal range prior to initiation of specific allergen injection immunotherapy (SIT), but all subsequent values have been elevated.

otherwise unremarkable. The patient's only medication was a daily multivitamin. SIT for allergic rhinitis had been initiated 9 months prior to presentation but was discontinued shortly after the initial finding of abnormal liver enzymes.

Laboratory evaluation from our center included a repeat liver panel with an AST of 138 U/L (normal 12–31 U/L) and other liver enzymes normal. Complete blood count, prothrombin time, creatine kinase, and thyroid-stimulating hormone level were normal. Additional serologic workup including ceruloplasmin, alpha-1 antitrypsin level and phenotype, serum protein electrophoresis, quantitative immunoglobulins, antiendomysial antibody, tissue transglutaminase antibody, and antimitochondrial antibody were all in the normal range. A repeat ASMA titer was also negative. The outside abdominal ultrasound was reviewed by our center's radiologists and interpreted as being within normal limits.

The patient was offered a 6-month period of observation as an alternative to liver biopsy. However, he strongly wished to resume SIT as soon as possible, and as there was some question as to whether SIT may have been playing a role in his AST elevation, the patient opted for liver biopsy after careful discussion. Biopsy revealed only minimal nonspecific changes.

The constellation of normal laboratory, imaging, and pathology studies and the absence of evidence for liver disease led to suspicion of the presence of macro-AST in this patient. Electrophoresis performed by Mayo Medical Laboratories (Rochester, MN) subsequently confirmed the diagnosis, with approximately 95% of the patient's total serum AST made up of macro-AST.

The patient resumed SIT after discussing these findings with his allergist. Serum for AST was again obtained 5 months after presentation and remained elevated at 75 IU/L (normal <40 IU/L).

DISCUSSION

Elevation of AST in the absence of muscle injury or myopathy most commonly represents hepatocellular injury. However, it is now acknowledged that a limited number of patients may develop AST elevation as a result of macro-AST formation. While the majority of reported patients have been asymptomatic (10–15), patients have been described with acute and chronic hepatitis including autoimmune hepatitis, ulcerative colitis, immunoblastic lymphadenopathy, primary and secondary hepatic malignancy, other gastrointestinal malignancy, myocardial infarction, and an unspecified autoimmune disorder among others (4–8, 16–18). However, any direct association between the presence of macro-AST and a particular disorder remains speculative in the absence of adequately powered population studies of macro-AST prevalence.

The pathogenesis of macroenzyme formation is unknown. Family studies of patients with macroamylasemia and cord blood studies have not supported a genetic component to the disorder (19). As such, 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 cross-reacts with an antibody that initially formed against a foreign antigen. A second theory is the “dysregulation of immune tolerance,” such as may occur in autoimmune disorders, though few reported patients with macro-AST have had evidence of other autoimmune diseases (3).

SIT exerts its effects through the development of immune tolerance via suppression of immunoglobulin E (IgE) by both T-cell and B-cell mechanisms. SIT is associated with an increase in allergen-specific IgG production by B cells; in other words, formation of IgE-specific IgG against the target allergen. As such, cross-reaction between this IgG and a self-antigen would appear plausible. Recognized side effects of SIT include local injection site reactions and occasional systemic reactions including asthma exacerbation and rarely anaphylactic shock (9). However, a literature search yielded no information on the potential for autoantibody formation as a consequence of SIT.

Our patient had documented normal AST 10 months prior to starting SIT and had no prior history of AST elevation over many years of undergoing regular physicals and screening laboratory evaluations. Seven months after beginning SIT for his allergic rhinitis, the patient was found to have elevated AST and it has remained elevated to varying degrees on each subsequent evaluation. As a result, we speculate that the patient may have formed a macroenzyme as a consequence of molecular mimicry—that is, a cross-reaction between the IgG formed against the allergen and the patient's AST enzyme.

AST levels in patients with macro-AST have been shown to fluctuate over time and may in fact be normal at times despite the continued presence of the macroenzyme in serum (8, 20). As such, we cannot be certain that macro-AST was not present prior to the initiation of SIT in our patient. As stated above, however, the patient had many previous screening laboratory evaluations and was unaware of any prior abnormal liver enzymes. In addition, electrophoresis revealed almost all of the patient's AST to be in the macroenzyme form, which further supports its more recent development.

In conclusion, we report a case of macro-AST discovered after the initiation of SIT for allergic rhinitis in an otherwise healthy patient. We propose that the development of a macroenzyme in this case may have been the result of antibody cross-reaction related to the SIT. Knowledge of this potential mechanism of macroenzyme development may be helpful in the evaluation of patients with isolated elevation in AST. As this has not previously been reported, it is unknown whether other macroenzymes may be capable of forming under similar conditions.

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