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## Isolated elevated aspartate aminotransferase in an asymptomatic woman due to macro-aspartate aminotransferase: A case report

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### Abstract

#### BACKGROUND

Macro-aspartate aminotransferase (AST), a macroenzyme, is a high-molecular mass complex formed by self-polymerization or association with other serum components that are difficult for the kidney to clear, leading to the isolated elevation of serum AST activity. Cases of macro-AST formation are rare, with only 3 published in the English language literature up to September 2019 in China. In this paper, we present a case in which an asymptomatic woman with persistent isolated elevated AST was confirmed as having macro-AST by the polyethylene glycol precipitation method.

#### CASE SUMMARY

A 34-year-old woman was referred to our clinic for elevated AST levels with normal levels of other liver-associated enzymes on November 12, 2018. Her AST level of liver function test had been abnormal for 7 mo before she came to the clinic. The patient was asymptomatic with a normal physical examination. There was no relevant family history and no alcohol consumption or smoking. She had a several-month history of traditional Chinese medical taking and had stopped it 1 year prior. The laboratory tests in our clinic showed only the elevation of AST (89.5 U/L) with no other significant abnormalities. We performed the precipitation technique with polyethylene glycol to confirm the presence of macro-AST. Then for almost a year, her AST level still fluctuated in the abnormal range.

#### CONCLUSION

This case highlights that clinical physicians should be familiar with this rare condition of persistent isolated AST elevation due to the presence of macro-AST to avoid unnecessary investigation and patient anxiety.

**Key words:** Aspartate aminotransferase; Macroenzymes; Macro-aspartate aminotransferase; Polyethylene glycol precipitation method; China; Case report

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**Core tip:** Here, we present a case in which an asymptomatic woman with persistent isolated elevated aspartate aminotransferase was diagnosed as having macro-aspartate aminotransferase, which was confirmed by the polyethylene glycol method; only 3 such cases have been published in the English language literature up to September 2019 in China. It is necessary for physicians to be sufficiently familiar with this condition to avoid repeated unnecessary check-ups.

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## INTRODUCTION

The elevation of liver enzymes is usually associated with liver injury, and both elevated aspartate aminotransferase (AST) and alanine aminotransferase are observed in most situations. However, the isolated elevation of AST with an unexplained cause can be found in some rare instances. At such cases time, the presence of macro-AST should be the one of suspected diagnoses. Macro-AST is a high molecular mass complex formed by AST with immunoglobulin or other plasma components<sup>[1]</sup>. As a benign etiology of isolated AST elevation, it is often ignored in clinical practice, leading to costly, unnecessary, or even invasive tests before diagnosis. Macro-AST can be detected by gel filtration chromatography, ultracentrifugation and precipitation with polyethylene glycol (PEG) or simply storage at 4 °C<sup>[2]</sup>. Here, we report a woman in China with persistent isolated elevated AST due to the presence of macro-AST.

## CASE PRESENTATION

### Chief complaints

A 34-year-old previously healthy woman was referred to our clinic with isolated elevated AST but had no symptoms on November 12, 2018.

### History of present illness

The patient was an infertile woman who found her liver function abnormal after a health examination for *in vitro* fertilization 7 mo before she came to our clinic. The liver function indicated that the only abnormal result was isolated elevated AST ranging from 76.2 to 170 U/L (reference range 13-35 U/L) with other liver-associated enzymes at normal levels during the past 7 mo. She had taken liver protection drugs intermittently but they had no effect.

### History of past illness

The patient had no significant medical history.

### Personal and family history

She had a history of taking traditional Chinese medical for her infertility but had stopped 1 year prior. There was no relevant family history or alcohol consumption.

### Physical examination upon admission

The physical examination of the patient showed no significant abnormality.

### Laboratory examinations

The laboratory tests showed only the elevation of AST (89.5 U/L), with normal levels of the other liver function tests and enzymes: Alanine aminotransferase: 16.1 U/L (7.0-40.0), alkaline phosphatase 47.6 U/L (35.0-100.0),  $\gamma$ -glutamyl transpeptidase 12.6 U/L (7.0-45.0), bilirubin 9.4  $\mu$ mol/ (6.8-30.0), and total protein 74.9 g/L (65.0-85.0). Serologic testing for viruses was negative and just anti-hepatitis B surface antibody was positive, with a titer of 1300.973 IU/L (the patient had been vaccinated against hepatitis B 3 years prior). Regarding the autoimmune aspect, we did not find

significant changes. Her ceruloplasmin, iron concentrations, and thyroid function test were also normal. The details and other laboratory data are shown in [Table 1](#).

### **Imaging examinations**

The abdominal ultrasonography showed mild cholecystitis.

### **Further diagnostic work-up**

We told the patient to stop taking so-called “liver protectors” and undergo regular reexaminations. During the following 7 mo, there was still a persistent elevation of AST ([Figure 1](#)), with normal values for the other liver function tests. Because of the lack of symptoms and lack of evidence of underlying causes such as liver, muscle, or cardiac disease, we suspected the diagnosis of macro-AST formation.

Hence, we decided to confirm the presence of macro-AST in our hospital laboratory by measuring whether AST activity decreased in the sample after PEG precipitation. For the study, we requested a new sample from the patient and used two serum samples from other patients with elevated AST as controls. We conducted the precipitation with PEG following a previously described method<sup>[3,4]</sup>. The activity of AST dropped sharply to 1.4 U/L after the process ([Table 2](#)). After 2 mo, the patient had a reexamination of her liver function, which showed that the AST was still abnormal.

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## **FINAL DIAGNOSIS**

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According to these results, we concluded that the isolated elevation of AST was most likely due to the presence of macro-AST.

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## **TREATMENT**

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There is no specific treatment for the patient because macro-AST is generally a benign condition.

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## **OUTCOME AND FOLLOW-UP**

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The patient remained healthy without any abnormalities, except for the isolated elevated AST.

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## **DISCUSSION**

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Macroenzymes are serum high molecular weight compounds formed by complexes of enzymes and their polymerization products. The enzymes are usually linked to immunoglobulins (mainly Ig G and Ig M) or other plasma components, which make their clearance slower and more difficult *via* urine, and ultimately lead to higher levels of their activity<sup>[3,5]</sup>. Macro-AST is one type of macroenzyme, which was first reported by Konttinen in 1978 in two healthy women<sup>[6]</sup>. This gradually led to the recognition that macro-AST may be one of the causes of elevated serum AST levels.

Macro-AST is rare, and the exact prevalence rate in the general population is unknown. There have been reports that the prevalence rate of macro-AST was 0.014% in 7273 patients who visited one hospital, while the prevalence was 9.09% in patients with isolated increased AST activity without liver abnormalities<sup>[4]</sup>. In addition, macro-AST seems to be more common in female patients < 60-years-old<sup>[7,8]</sup>, which is also a high-risk group for autoimmune diseases. As described in the previous literature, the mechanism of the immune complex formation may be due to autoimmunity. The immune reaction or the dysregulation of immune tolerance seems to be associated with immune complex formation<sup>[9]</sup>.

To the best of our knowledge, there are very few reports on macro-AST in China. Our patient is a female of child-bearing age who belongs to a high-risk group<sup>[6]</sup>. The increased serum activities of AST usually result from liver, heart, skeletal muscle, and erythrocyte injury. Our patient had no evidence of hepatic disease, skeletal muscle disorders, myocardial disease, or hemolysis according to the evaluations with abdominal imaging studies and laboratory examinations. Therefore, after a literature review, the presence of benign macroenzymes became suspected in the absence of organ-specific disease. Ultimately, we performed an experiment with PEG that clearly demonstrated the presence of macro-AST. Prior to being referred to our clinic, our

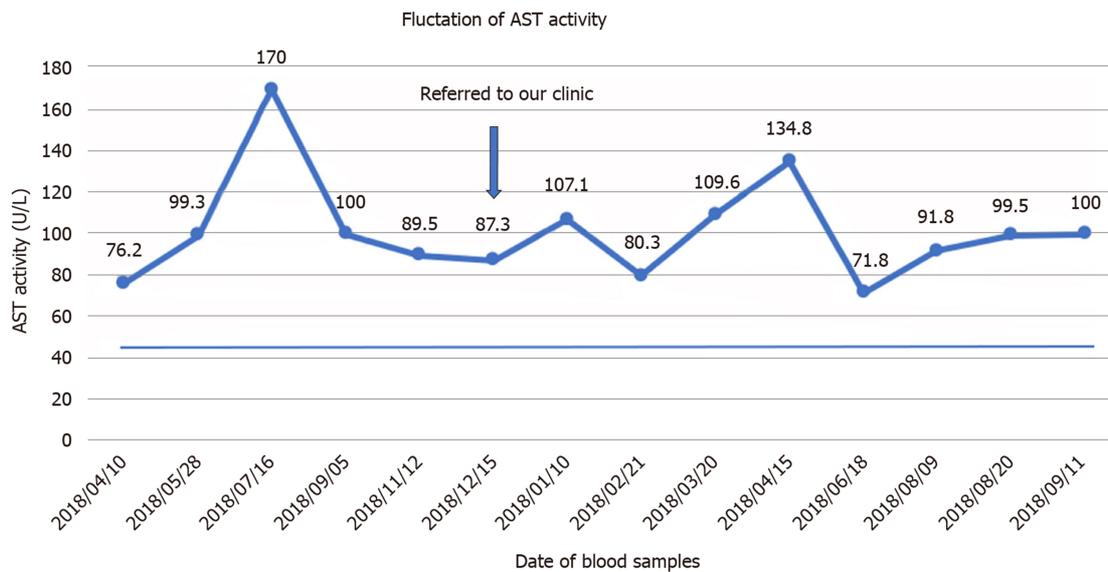
Table 1 Laboratory data in the clinic

Parameter	Result (normal range)	Parameter	Result (normal range)
AST in U/L	89.5 (13.0-35.0)	WBC as $\times 10^9/L$	4.49 (3.5-9.5)
ALT in U/L	16.1 (7.0-40.0)	RBC as $\times 10^9/L$	4.22 (3.8-5.10)
GGT in IU/L	12.6 (7.0-45.0)	Hemoglobin in g/L	123 (115-150)
ALP in IU/L	47.6 (35.0-100.0)	Platelets as $\times 10^9/L$	187 (125-350)
ACHE in IU/L	7194 (4300-12000)	Neutrophils as $\times 10^9/L$	2.69 (1.80-6.30)
TP in g/L	74.9 (65.0-85.0)	Lymphocytes as $\times 10^9/L$	1.41 (1.10-3.20)
ALB in g/L	44.9 (40.0-55.0)	Monocytes as $\times 10^9/L$	0.32 (0.10-0.60)
GLB in g/L	30.0 (20.0-40.0)		
TBIL in $\mu\text{mol/L}$	9.4 (6.8-30.0)	CHOL in mmol/L	4.39 (2.6-6.0)
DBIL in $\mu\text{mol/L}$	2.8 (0.0-8.6)	TG in mmol/L	0.62 (0.28-1.80)
IBIL in $\mu\text{mol/L}$	6.6 (5.1-21.4)		
Enzyme parameter		Virology test	
CK in U/L	67 (40-200)	Anti-HAV-IgM	- (-)
CKMB in U/L	7.2 (0.0-25)	Anti-HEV-IgM	- (-)
LDH in U/L	161 (120-250)	HBsAg	- (-)
$\alpha$ -HBDH in U/L	116 (78.0-182.0)	Anti-HBsAb	+ (-)
MAO in U/L	3.4 (0.0-12.0)	HBeAg	- (-)
AFU in U/L	21 (3.0-40.0)	Anti-HBeAb	- (-)
AMY in U/L	90 (1-135)	Anti-HBeAb	- (-)
LPS in U/L	46 (5.6-51.3)	Anti-HCV	- (-)
		Anti-HIV	- (-)
Immunological test		Anti-TP	- (-)
Anti-dsDNA	- (-)		
Anti-M2	- (-)	Liver metabolism test	
Anti-gp210	- (-)	CER in g/L	0.28 (0.2-0.6)
Anti-SP100	- (-)	SI in $\mu\text{mol/L}$	15.6 (7.8-32.2)
Anti-SSA-52/Ro52	- (-)	SF in $\mu\text{mol/L}$	43.5 (10-120.0)
Anti-Sm	- (-)	TIBC in $\mu\text{g/L}$	62.0 (50.0-70.0)
Anti-nRNP/Sm	- (-)		
Anti-LKM	- (-)		
Immunoglobulin A in g/L	2.60 (0.7-4.0)		
Immunoglobulin G in g/L	15.1 (7.0-16.0)		
Immunoglobulin M in g/L	0.90 (0.4-2.3)		
Complement C3 in g/L	1.31 (0.9-1.8)		

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT:  $\gamma$ -glutamyltransferase; ALP: Alkaline phosphatase; ACHE: Acetylcholinesterase; TP: Total protein; ALB: Albumin; GLB: Globulin; TBIL: Total bilirubin; DBIL: Direct bilirubin; IBIL: Indirect bilirubin; CK: Creatine kinase; CKMB: Creatine kinase isoenzymes; LDH: Lactate dehydrogenase;  $\alpha$ -HBDH:  $\alpha$ -Hydroxybutyrate Dehydrogenase; MAO: Monoamine oxidase; AFU:  $\alpha$ -L-Fucosidase; AMY: Amylase; LPS: Lipase; Anti-dsDNA: Anti-double strand DNA antibody; Anti-M2: Antimitochondrial antibody 2; Anti-Sm: Anti-smooth muscle antibody; WBC: White blood cells; Anti-LKM: Anti liver and kidney microsomes antibody; WBC: White blood cell; RBC: Red blood cells; CHOL: Cholesterol; TG: Triglyceride; anti-HCV: Anti-hepatitis C virus antibody; anti-HIV: Anti-human immunodeficiency virus antibody; Anti-TP: Anti-Treponema pallidum; CER: Ceruloplasmin; SI: Serum iron; SF: Serum ferritin; TIBC: Total iron binding capacity.

patient underwent many repeated check-ups and was even advised to undergo a liver biopsy because elevated AST was observed. Moreover, she had been treated with various liver protective drugs that had no effect on her. She experienced significant psychological stress.

To date, whether macro-AST is related to disease is unsure and has attracted much attention. Although it has been reported that macroenzymes have been associated with various conditions, such as rheumatoid arthritis or other autoimmune conditions, allergen injection immunotherapy, monoclonal gammopathy, and chronic hepatitis C or possibly resolved acute hepatitis C<sup>[10]</sup>, the majority of reported cases are asymptomatic. There is a report that the AST activity of a young woman with macro-AST for 12 years fluctuated between 163 and 500 U/L but she still remained healthy<sup>[8]</sup>. In addition, there have been 3 cases of macro-AST patients reported in China who remained healthy after 2-7 years of follow-up<sup>[11]</sup>. Two studies in children with macro-



**Figure 1** Changes in the patient's aspartate aminotransferase activity over a 17-mo period. The horizontal bar represents the upper limit of normal of aspartate aminotransferase (AST).

AST showed that all children remained healthy during long-term follow-up<sup>[12]</sup>, and these studies have shown that macro-AST is a benign condition that needs no further work-up. In addition, a study showed that familial isolated elevated AST may be associated with a heterozygous mutation in glutamate oxaloacetate transaminase 1<sup>[13]</sup>.

Macro-AST can be detected by multiple methods; the most common are precipitating the complexes of macroenzymes with PEG or simply storing the sample at 4 °C, which is convenient and economical, although two cases reported by Chtioui *et al*<sup>[14]</sup> in 2010 and Maan *et al*<sup>[15]</sup> in 2017 showed no significant decrease in AST levels after 1 wk of being stored at 4 °C. Ultracentrifugation and gel filtration chromatography, which constitute the standard reference method, require highly specialized chromatography, are complex and relatively expensive and are not available in most clinical laboratories. In the samples from our patient, we performed a precipitation technique with PEG to confirm the presence of macro-AST. After the patient's serum was treated with PEG, immunoglobulins precipitated out, revealing the lower free AST concentration. PEG precipitation confirmed the presence of macro-AST with 96.4% polyethylene glycol precipitable activity, which was significantly greater than in the controls.

## CONCLUSION

In conclusion, although macro-AST is rare, clinicians and laboratories should consider macro-AST as a cause of unexplained isolated AST elevations if the patients are asymptomatic and other diseases causing an increase in AST have been excluded. A high index of suspicion may help reduce costs and patient anxiety before performing additional tests.

**Table 2** Precipitation with polyethylene glycol

	AST origin	AST DIL1/2	AST PEG	PPA (%)	AST recovery (%)
Patient	71.8	38.9	1.4	96.4	3.60
Control 1	229	121.7	49.8	59.1	40.9
Control 2	68	31	17.7	42.9	57.1

Polyethylene glycol precipitation (PEG): 25% PEG centrifuged at 3000 rpm of two control serum samples and samples from the patient with macro-aspartate aminotransferase (AST). AST origin: AST value of the original serum; AST diluted 1/2 (DIL1/2): AST value of serum DIL1/2 with phosphate-buffered saline; AST PEG: AST value after PEG precipitation. PEG-precipitable activity (PPA) =  $100 \times [(AST\ DIL1/2 - AST\ PEG) / AST\ DIL1/2]$ ; AST recovery =  $100 \times (AST\ PEG / AST\ DIL1/2)$ .

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