A case of macroenzyme aspartate aminotransferase (macro-AST) in a patient with seronegative rheumatoid arthritis

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Aspartate aminotransferase (AST) is commonly measured as part of a liver function test panel. Although elevations in AST may indicate hepatic disease, AST elevations are not as liver specific as alanine aminotransferase (ALT) elevations, and they are also associated with myositis, rhabdomyolysis, acute myocardial infarction or haemolysis. Although not widely recognised by physicians, macroenzyme aspartate aminotransferase (macro-AST) caused by immunoglobulin binding to AST is also as an uncommon cause of AST elevation.

Case report

A 19-year-old female Caucasian patient with probable seronegative rheumatoid arthritis, with pain in her wrists, fingers and ankles and with associated stiffness, came to our attention following five weeks of consistently raised AST on three separate occasions (260–288 U/L (Reference Interval (RI): 0–50)). This was in the setting of otherwise normal liver function tests that were performed before commencing sulfasalazine. AST was measured using the Abbott ARCHITECT c16000. AST seven months previously was 28 U/L.

A number of investigations were performed to determine the cause of elevated AST, including measurement of creatine kinase (CK) and abdominal ultrasound, as well as a miscellaneous screen for causes of liver disease. AST recovery post polyethylene glycol (PEG) precipitation was determined to investigate for macro-AST. For this, 200 µL of 24% PEG 6,000 was added to 200 µL of patient sample, incubated at 20 minutes at 37°C and centrifuged at 3,000 rpm for five minutes. 200 µL of supernatant was diluted with 200 µL of 0.9% sodium chloride and vortexed before analysis for AST. The resulting AST was multiplied by four to account for dilution.

Results

The post-PEG recovery of AST was less than 4%, compared with 48% in a control patient, strongly suggestive of macro-AST (Table 1).

Normal CK (89 U/L (RI: 30–180)) suggested no substantial muscular source to explain elevated AST. Abdominal ultrasound demonstrated normal liver. Iron studies demonstrated iron deficiency rather than overload, with a transferrin saturation of 7% (RI: 16–45), and a ferritin of 49 µg/L (RI: 20–200) in context of a CRP of 11 mg/L (RI: <5). Caeruloplasmin was normal (0.47 g/L (RI: 0.15–0.60)). Alpha-1 antitrypsin had normal MM phenotype and level (2.9 g/L (RI: 1.0–2.0)). Alpha-fetoprotein was not elevated (<5 µg/L (RI: 0–16)). Hepatitis B and C serologies were negative. Anti-nuclear antibodies (ANA) were detected at 1:320 in a homogeneous, chromosome positive pattern (Table 2). Haemolysis was not considered likely, with a haemoglobin of 130 g/L and bilirubin of 5 µmol/L.

Due to analyser changeover in our laboratory, AST was subsequently found to be elevated on the Beckman Coulter AU5800. Interestingly, our patient's AST normalised nine months following the initial presentation (Figure 1).

Discussion

We describe a case of macro-AST in a patient with probable seronegative rheumatoid arthritis, supported by low post-PEG recovery of AST, and substantial exclusion of muscular or liver related causes of AST elevation.

Macro-AST is caused by immunoglobulin bound to AST, leading to decreased clearance of AST and elevated levels of AST in the plasma. Immunoglobulin G (IgG), immunoglobulin A (IgA) and immunoglobulin M (IgM) bound to AST have all been described.[1–8] Macro-AST is generally benign.

Table 1: Low post-PEG recovery of AST in case vs control sample indicative of macro-AST.

Sample	Pre-PEG AST (U/L)	Post-PEG AST (U/L)	% Recovery post-PEG
Current patient	291	<12	<4%
Control sample	233	112	48%

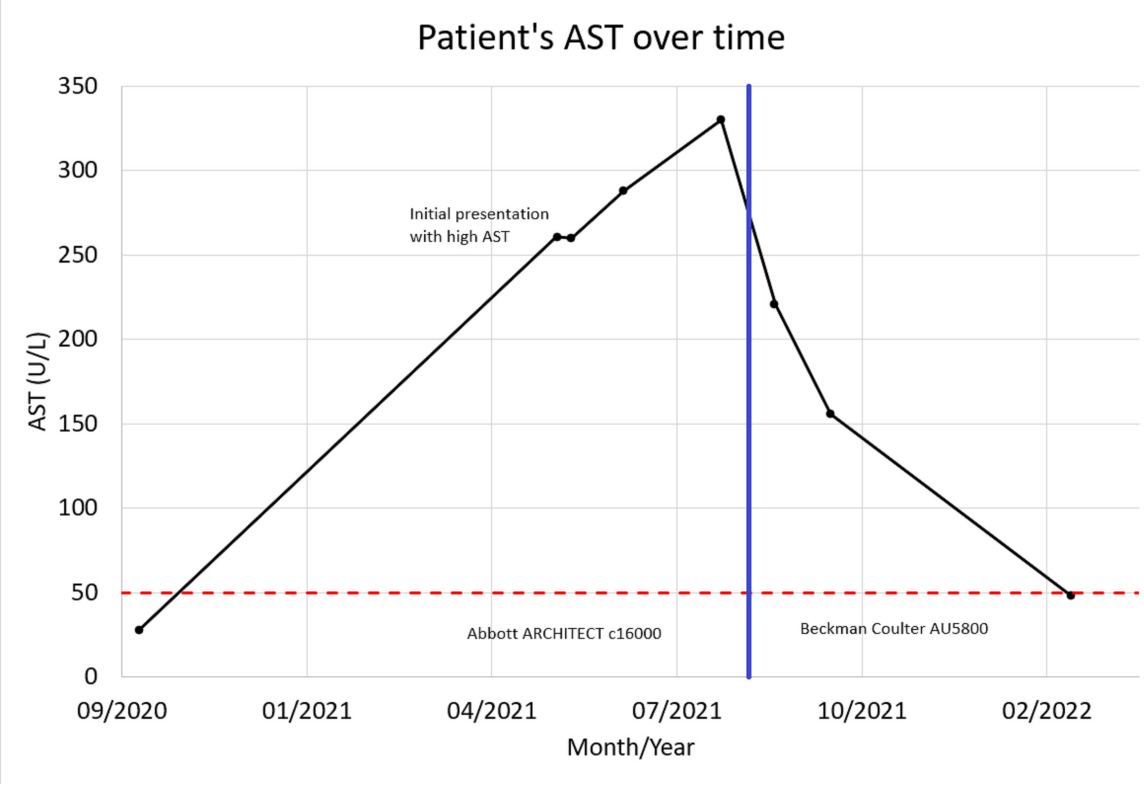
Table 2: Biochemistry of patient.

Biochemistry	Result	Reference Interval
Albumin	38 g/L	32–48
Bilirubin	5 µmol/L	2–20
Alkaline phosphatase (ALP)	76 U/L	30–150
Gamma-glutamyl transferase (GGT)	14 U/L	10–35
Aspartate aminotransferase (AST)	260 U/L	10–50
Alanine aminotransferase (ALT)	**24 U/L**	**0–30**
C-reactive protein (CRP)	11 mg/L	<5
Hepatitis C antibody	Negative	Negative
Hepatitis B surface antigen	Negative	Negative
Hepatitis B surface antibody	Negative	
Hepatitis B core antibody	Negative	Negative
Transferrin saturation	7%	16–45
Ferritin	49 µg/L	20–200
Creatine kinase	89 U/L	30–180
Glycated haemoglobin (HbA1c)	29 mmol/mol	20–40 mmol/mol
Copper	27.5 µmol/L	11.3–25.2
Caeruloplasmin	0.47 g/L	0.15–0.60
Alpha-1 antitrypsin level	2.9 g/L	1.0–2.0
Alpha-1 antitrypsin phenotype	MM	MM
Alpha-fetoprotein (AFP)	<5 µg/L	0–16
Immunoglobulin G (IgG)	14.5 g/L	7.0–14.0
Immunoglobulin A (IgA)	0.8 g/L	0.8–3.5
Immunoglobulin M (IgM)	0.5 g/L	0.5–2.0
Autoantibody screen		
Anti-nuclear antibody	1:320, homogeneous, chromosome positive	None detected
Smooth muscle	None detected	None detected
Mitochondrial antigens	None detected	None detected
Liver Kidney Microsomal	None detected	None detected

Although its pathogenesis is unclear, there have been other case reports of macro-AST in association with rheumatological conditions in the literature, hypothesised to be due to dysregulation of immune tolerance.[3,4] Prevalence is reported as 22–38.6% of paediatric patients with persistently isolated elevated AST, and 13.1% of adult patients with elevated AST and AST/ALT ratio.[5–7]

Macro-AST is an under recognised cause of AST elevation. In the appropriate clinical setting, an isolated elevation in AST should lead to correspondence with the laboratory to enable relevant studies to investigate the diagnosis of macro-AST. In some patients, macro-AST resolves spontaneously with time.[5] A percent precipitable activity ≥75% (i.e., post-PEG recovery ≤25%) was previously found to be the optimal threshold for determining macro-AST using 24% PEG 6,000.[5] Beyond PEG precipitation, other methods to prove macro-AST include gel filtration chromatography, ultrafiltration and Protein A or G immunodepletion (if it is an IgG macroenzyme).[5,8] Recognition of macro-AST as the cause of elevated AST is critical to avoid misattribution of elevated AST and avoid unnecessary invasive investigations.

Figure 1: Change in patient's AST over time. Upper reference limit indicated as the horizontal dashed line (50 U/L) and analyser changeover indicated by a solid vertical line.



COMPETING INTERESTS
Nil.

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REFERENCES
1. Tameda M, Shiraki K, Ooi K, et al. Aspartate aminotransferase-immunoglobulin complexes in patients with chronic liver disease. World J Gastroenterol. 2005;11(10):1529-1531.
2. Rubin A S, Sass D A, Stickle D F. Distribution of serum concentrations reported for macroenzyme aspartate aminotransferase (macro-AST). Pract Lab Med. 2017;8:65-69.
3. Mbagaya W, Foo J, Luvai A, et al. Persistently raised aspartate aminotransferase (AST) due to macro-AST in a rheumatology clinic. Diagnosis (Berl). 2015;2(2):137-140.
4. Rohani P, Imanzadeh F, Sayyari A, et al. Persistent elevation of aspartate aminotransferase in a child after incomplete Kawasaki disease: a case report and literature review. BMC Pediatr. 2020;20(1):73.
5. Caropreso M, Fortunato G, Lenta S, et al. Prevalence and long-term course of macro-aspartate aminotransferase in children. J Pediatr. 2009;154(5):744-748.
6. Magen-Rimon R, Tal G, Kaplan M, Shaoul R. The significance of isolated aspartate aminotransferase elevation in healthy paediatric patients. Acta Paediatr. 2022;111(3):675-679.
7. Moriyama T, Nobuoka M, Makino M. Incidence and properties of aspartate aminotransferase-immunoglobulin complexes in patients with a high serum aspartate to alanine aminotransferase ratio. Clin Chim Acta. 1990;190(1-2):47-56.
8. van Wijk X M R, Magee C A, Wu A H B, et al. A comparison of methods for evaluation of a case of suspected macro-aspartate aminotransferase. Clin Chim Acta. 2016;463:1-3.