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# 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Antibody-Positive Immune-Mediated Necrotizing Myopathy With Transaminitis and Nonspecific Liver Biopsy Findings in a Statin-Naive Patient

John T. Meghreblian <sup>1</sup>, Abigail N. Horrar <sup>1</sup>, Benjamin E. Jewett <sup>2</sup>

1. Internal Medicine, East Tennessee State University, Johnson City, USA 2. Medical Education, Ballad Health, Johnson City, USA

**Corresponding author:** Abigail N. Horrar, horrar@etsu.edu

## Abstract

Anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) immune-mediated necrotizing myopathy (IMNM) causes proximal weakness and marked creatine kinase (CK) elevation. Serum aminotransferases may also increase with muscle injury and be mistaken for primary liver disease. We describe a 64-year-old man without statin exposure who developed five months of progressive proximal weakness and weight loss. CK and aminotransferases were markedly elevated, and anti-HMGCR antibodies were strongly positive. Hepatitis and autoimmune liver testing were unrevealing; liver biopsy showed mild nonspecific changes. Pulse methylprednisolone, intravenous immunoglobulin (IVIG), and a prednisone taper produced early functional improvement. Alanine aminotransferase (ALT) normalized by approximately 6 months and aspartate aminotransferase (AST) by approximately 13 months, whereas CK first returned to its reference interval at approximately 18 months and remained normal at approximately 21 months. The clinical phenotype, severe hyperCKemia, anti-HMGCR seropositivity, magnetic resonance imaging findings, and longitudinal biochemical response favored a major skeletal muscle contribution to the aminotransferase elevation, although a concurrent mild hepatic process could not be definitively excluded; the biopsy did not demonstrate anti-HMGCR-mediated hepatic injury. Early CK measurement in patients with proximal weakness and transaminitis can clarify the source, while liver evaluation remains appropriate when supported by cholestatic markers, synthetic dysfunction, imaging, or histology.

**Categories:** Neurology, Rheumatology, Endocrinology/Diabetes/Metabolism

**Keywords:** anti-hmgcr, creatine kinase, immune-mediated necrotizing myopathy, liver biopsy, statin-naive, transaminitis

## Introduction

3-Hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) catalyzes the rate-limiting step in cholesterol synthesis. It is highly expressed and regulated in the liver and is upregulated in regenerating myofibers, a finding that may help sustain autoimmunity after a statin trigger is removed [1-3]. In anti-HMGCR immune-mediated necrotizing myopathy (IMNM), circulating immunoglobulin G (IgG) autoantibodies recognize the intracellular enzyme, and complement activation at the myofiber surface drives the myonecrosis and regeneration that define the disease; because HMGCR is upregulated in regenerating myofibers, the autoimmune response can become self-perpetuating even after a statin trigger is withdrawn [1-3].

Anti-HMGCR IMNM usually presents with subacute, symmetric proximal weakness and marked creatine kinase (CK) elevation. Statin exposure is common but not required. In a 45-patient European cohort, 55.6% were statin-naive [4]; a Chinese series described 21 statin-naive patients [5]; and a registry study found prior statin use in only 2 of 13 anti-HMGCR-positive patients [6]. A recent multinational study estimated an adult incidence of 2.9 cases per million person-years [7].

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) are released from injured skeletal muscle and are elevated in roughly 80% of patients with inflammatory myopathy, typically rising and falling in parallel with CK [8-10]. Active myonecrosis can therefore resemble hepatocellular injury and prompt a liver-directed evaluation, including liver biopsy, before a muscle source is considered. Gamma-glutamyl transferase (GGT), by contrast, is not released by injured skeletal muscle and is the more specific discriminator of true hepatic injury [10].

This case examines statin-naive anti-HMGCR IMNM in which aminotransferase elevation was documented before recognized muscle weakness and a liver biopsy showed only nonspecific changes. The specific gap it addresses is the diagnostic implication of transaminitis that precedes clinically apparent weakness, together with the interpretation of nonspecific liver biopsy findings in this setting, a sequence that can anchor the

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evaluation on primary liver disease and delay recognition of myopathy.

## Case Presentation

### Patient history and presentation

A 64-year-old man was referred for five months of progressive proximal weakness and a 30-lb unintentional weight loss. Difficulty lifting heavy objects progressed to difficulty climbing stairs and bending. He denied myalgia, dysphagia, and dysarthria. Aminotransferase elevation had prompted a liver biopsy before CK was measured; a subsequently detected marked CK elevation led to neurology referral.

He had no history of statin exposure or diabetes. His medications were lisinopril and a multivitamin. He reported minimal alcohol use, no illicit drug use, and no smoking history.

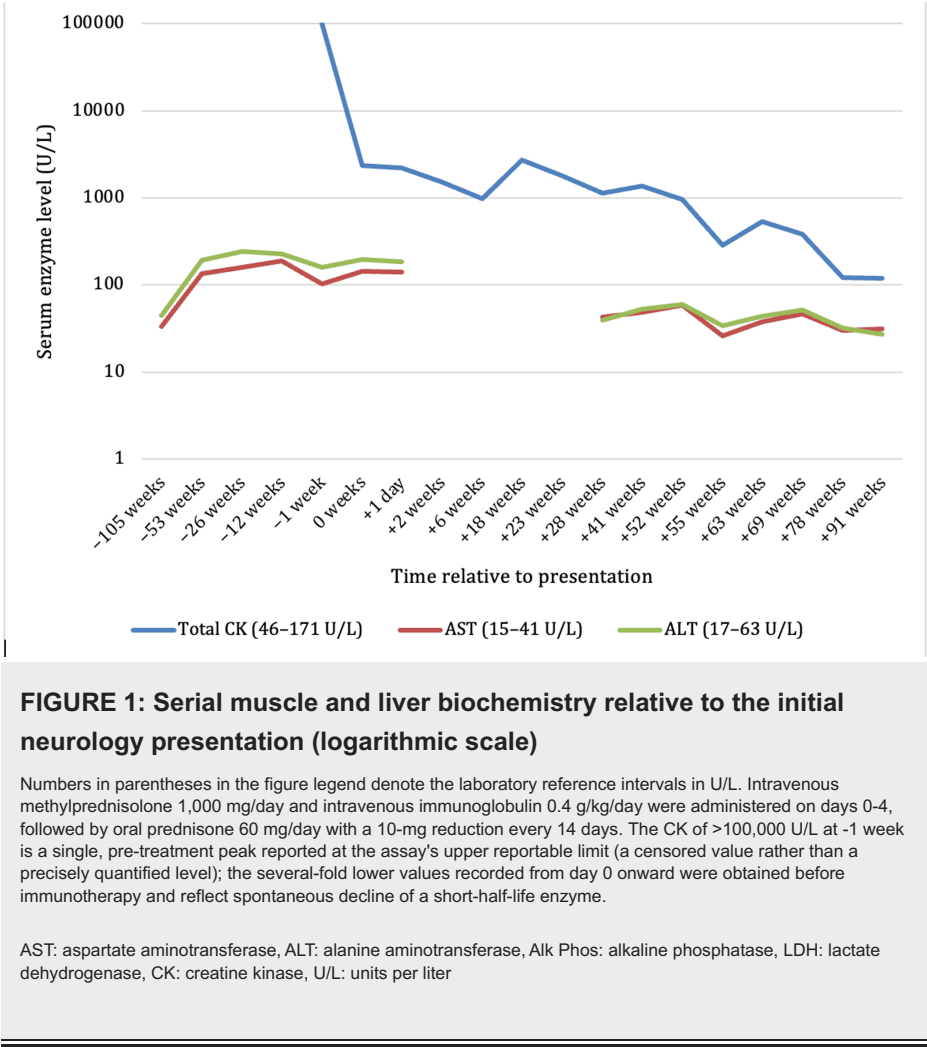
### Physical examination

At the initial neurologic evaluation, vital signs were normal, and body mass index was 21.3 kg/m<sup>2</sup>. Mental status and cranial nerve examinations were normal. Muscle bulk was diffusely reduced, with normal tone and no abnormal movements.

Manual muscle testing showed symmetric proximal weakness: deltoids were 4+/5 and hip flexors were 4-/5 bilaterally; all other tested muscle groups were 5/5. Vibration was reduced at the great toes, and muscle stretch reflexes were absent. Coordination and gait were normal.

### Diagnostic evaluation

AST and ALT were elevated before weakness began (Figure 1). Antimitochondrial M2 and anti-smooth-muscle antibodies and viral hepatitis testing were negative. A nonalcoholic steatohepatitis FibroSure panel (Labcorp, Burlington, NC) was within normal limits. Because the aminotransferase abnormalities were initially approached as possible liver disease, a percutaneous liver biopsy had been performed; histopathology demonstrated scattered lipofuscin pigment, lipid-laden histiocytes, and glycogenated nuclei, interpreted as consistent with resolving mild liver injury (Figure 2).



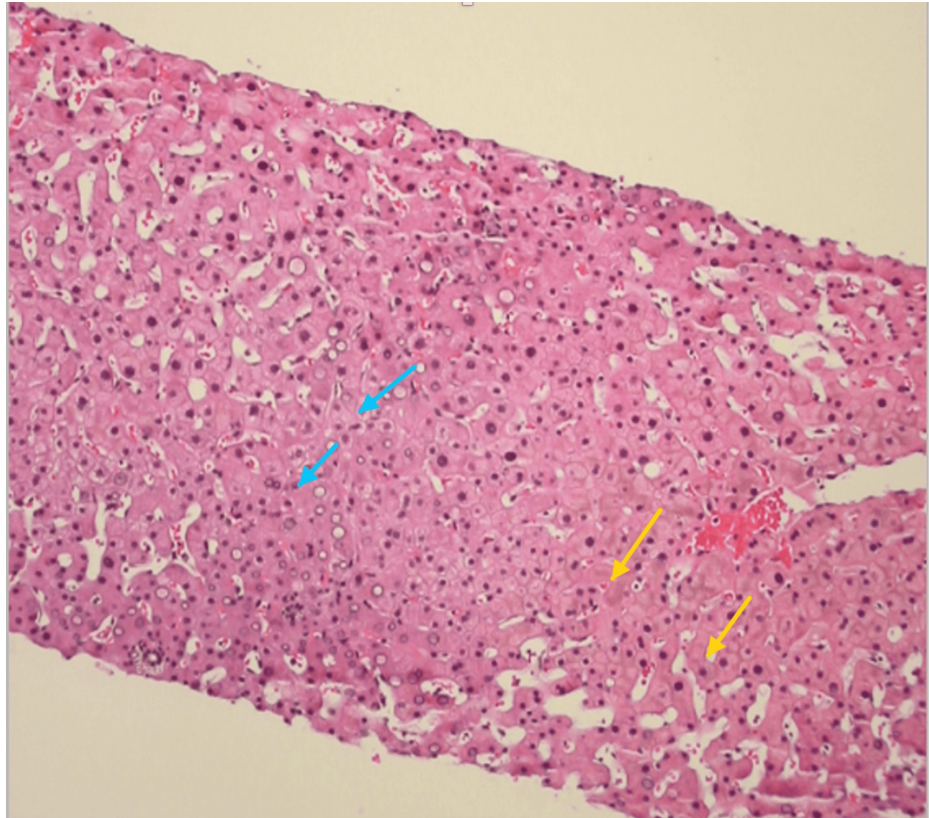


**FIGURE 2: Liver biopsy demonstrating scattered glycogenated nuclei and perivenular lipofuscin pigment**

Blue arrows indicate representative glycogenated nuclei; yellow arrows indicate representative perivenular lipofuscin pigment (hematoxylin and eosin stain, original magnification  $\times 100$ ).

The authors added the arrows to the original photomicrograph according to the issued pathology report; no other image content was altered.

Diagnostic laboratory investigations are summarized in Table 1.

| Test                                | Result               | Interpretation  | Reference interval or criterion                                                           |
|-------------------------------------|----------------------|-----------------|-------------------------------------------------------------------------------------------|
| Aldolase                            | 37.0 U/L             | High            | 3.3-10.3 U/L                                                                              |
| Anti-HMGCR antibody                 | >200 units           | Strong positive | Negative: <20 units, weak positive: 20-39, moderate positive: 40-59, strong positive: >59 |
| Anti-mitochondrial M2 IgG           | Negative             | Negative        | Negative                                                                                  |
| Anti-smooth-muscle (anti-actin) IgG | 2 units              | Negative        | 0-19 units                                                                                |
| Viral hepatitis panel               | Negative             | Negative        | Negative                                                                                  |
| NASH FibroSure panel                | Within normal limits | Normal          | Assay-specific                                                                            |

TABLE 1: Diagnostic laboratory investigations obtained before and during the neuromuscular evaluation

Antimitochondrial M2 IgG, anti-smooth-muscle (anti-actin) IgG, viral hepatitis testing, and the NASH FibroSure panel were obtained during the liver-focused evaluation before neurology referral. Aldolase was measured one week before the initial neurology presentation. Anti-HMGCR antibody testing was obtained during the subsequent neuromuscular evaluation.

HMGCR: 3-hydroxy-3-methylglutaryl-coenzyme A reductase, IgG: immunoglobulin G, NASH: nonalcoholic steatohepatitis, U/L: units per liter

Serial laboratory trends are summarized in Table 2.

| Time relative to presentation | AST (15-41 U/L) | ALT (17-63 U/L) | Alk Phos (34-104 U/L) | Aldolase (3.3-10.3 U/L) | LDH (U/L) (120-246 U/L) | Total CK (46-171 U/L) |
|-------------------------------|-----------------|-----------------|-----------------------|-------------------------|-------------------------|-----------------------|
| -105 weeks                    | 33              | 45              | 33                    | -                       | -                       | -                     |
| -53 weeks                     | 135             | 191             | 63                    | -                       | -                       | -                     |
| -26 weeks                     | 159             | 242             | 61                    | -                       | 807                     | -                     |
| -12 weeks                     | 189             | 229             | 69                    | -                       | -                       | -                     |
| -1 week                       | 103             | 158             | 68                    | 37                      | 890                     | >100,000              |
| Presentation (day 0)          | 143             | 196             | 75                    | -                       | -                       | -                     |
| +1 day                        | 141             | 186             | 78                    | -                       | -                       | 2,197                 |
| +2 weeks                      | -               | -               | -                     | -                       | -                       | 1,526                 |
| +6 weeks                      | -               | -               | -                     | -                       | -                       | 977                   |
| +18 weeks                     | -               | -               | -                     | -                       | -                       | 2,740                 |
| +23 weeks                     | -               | -               | -                     | -                       | -                       | 1,780                 |
| +28 weeks                     | 43              | 39              | 39                    | -                       | -                       | 1,133                 |
| +41 weeks                     | 49              | 53              | 49                    | -                       | -                       | 1,356                 |
| +52 weeks                     | 59              | 60              | 68                    | -                       | -                       | 967                   |
| +55 weeks                     | 26              | 34              | 67                    | -                       | -                       | 285                   |
| +63 weeks                     | 38              | 44              | 82                    | -                       | -                       | 535                   |
| +69 weeks                     | 47              | 52              | 63                    | -                       | -                       | 384                   |
| +78 weeks                     | 30              | 32              | 69                    | -                       | -                       | 122                   |
| +91 weeks                     | 31              | 27              | 58                    | -                       | -                       | 120                   |

**TABLE 2: Serial muscle and liver biochemistry relative to the initial neurology presentation**

Numbers in parentheses in the column headers are laboratory reference intervals; all reported laboratory values are in U/L. Negative time points precede the initial neurology visit. AST and ALT were documented before weakness began and declined after treatment; ALT normalized by approximately 6 months (+28 weeks) and AST by approximately 13 months (+55 weeks). CK first entered the stated reference interval at approximately 18 months and remained within range at approximately 21 months. The -1 week CK of >100,000 U/L was reported at the assay's upper reportable limit and represents a censored value. Alkaline phosphatase was not elevated, albumin was normal when measured, and total bilirubin was not elevated; none of these, nor gamma-glutamyl transferase or the international normalized ratio, were serially tracked.

AST: aspartate aminotransferase, ALT: alanine aminotransferase, Alk Phos: alkaline phosphatase, LDH: lactate dehydrogenase, CK: creatine kinase, -: not measured

Subsequent testing showed CK above the assay's upper reportable limit (>100,000 U/L), elevated aldolase, and a strongly positive anti-HMGCR antibody. This >100,000 U/L result was a single measurement obtained one week before presentation and was reported at the assay's upper reportable limit, a censored value rather than a precisely quantified level. The values of approximately 2,200-2,740 U/L recorded from day 0 onward were obtained before immunotherapy and reflect spontaneous fluctuation of an enzyme with a serum half-life on the order of 1.5 days, such that a markedly elevated peak can fall several-fold within a week once the rate of myonecrosis stabilizes. A comprehensive myositis antibody panel, including signal recognition particle and antisynthetase antibodies, was otherwise negative, as was cytosolic 5'-nucleotidase 1A antibody (anti-cN-1A) testing (Table 1). Thyroid-stimulating hormone and vitamin B12 were normal. Magnetic resonance imaging of the left thigh showed mild patchy edema and faint enhancement in the quadriceps, adductor, and hamstring compartments (Figure 3), interpreted as mild myositis.

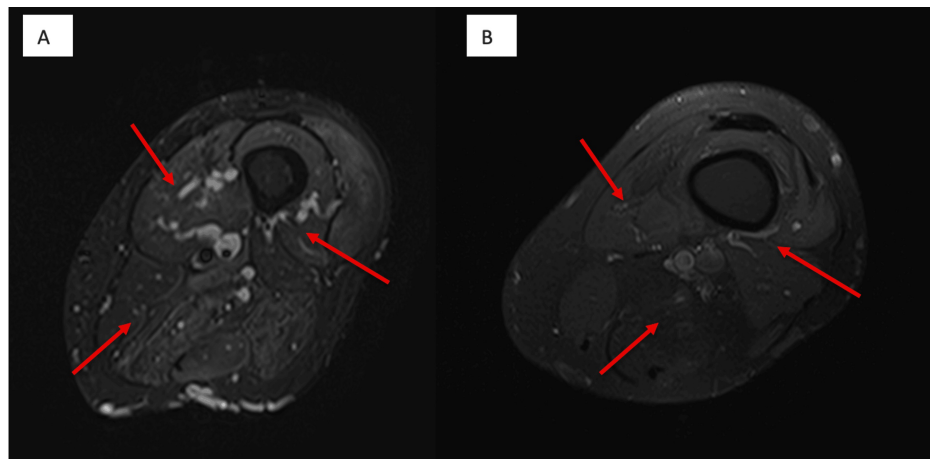


**FIGURE 3: Axial magnetic resonance imaging of the left thigh**

(A) STIR image demonstrating mild patchy intramuscular edema. (B) Contrast-enhanced T1-weighted image demonstrating faint corresponding intramuscular enhancement. The abnormal signal involved the quadriceps, adductor, and hamstring compartments and was interpreted as consistent with mild myositis.

STIR: short tau inversion recovery

The proximal pattern of weakness, marked CK elevation, strongly positive anti-HMGCR antibodies, and supportive magnetic resonance imaging findings supported a clinical diagnosis of anti-HMGCR IMNM. Electromyography was cancelled, and muscle biopsy was not performed because neither was expected to change management.

### Treatment and outcome

Treatment aimed to arrest immune-mediated muscle injury, restore proximal strength and function, and normalize CK while limiting prolonged glucocorticoid exposure. Induction therapy consisted of intravenous immunoglobulin (IVIG) 0.4 g/kg/day for five days (days 0-4) and intravenous methylprednisolone 1,000 mg/day for five days (days 0-4), and was followed by oral prednisone 60 mg/day for 14 days with a 10-mg reduction every 14 days. CK was monitored after the five-day induction and serially thereafter to guide therapy. Additional IVIG and rituximab were reserved for an inadequate response but were not administered.

The patient showed progressive improvement. Within a month, he reported feeling "a lot better" and resumed work around his homestead, with subjective improvement in hip flexor strength and mild insomnia as the only reported adverse effect. At approximately 10 weeks, he estimated 65% improvement. Hip flexors remained 4-/5, with 5/5 strength elsewhere. CK fell after induction, a decline consistent with the rapid, treatment-related reduction that can follow pulse methylprednisolone, and then rebounded during the prednisone taper and subsequently declined (Figure 1). ALT returned to its reference interval at 28 weeks (about 6 months) and AST at 55 weeks (about 13 months). CK first returned to its reference interval at 78 weeks (about 18 months) and remained normal at 91 weeks (about 21 months).

### Discussion

This case links statin-naïve anti-HMGCR IMNM with a liver-focused diagnostic pathway. Aminotransferase elevation was documented before weakness began, whereas the liver biopsy showed only mild nonspecific changes. The subsequent CK elevation, anti-HMGCR result, proximal weakness, and response to immunotherapy favored a predominantly muscle-derived contribution to the aminotransferases; however, a concurrent hepatic contribution cannot be completely excluded, particularly given the histologic changes interpreted as mild resolving liver injury.

Statin-naïve anti-HMGCR disease is well recognized. Allenbach et al. found no statin exposure in 55.6% of 45 patients; 97.7% had weakness, mean CK was 6,941 U/L, and weight loss occurred in 20% [4]. Jiao et al. described 21 statin-naïve patients with proximal and neck flexor weakness and a mean maximal CK of 7,968.6 U/L; 61.9% required an additional immunosuppressant and 38.1% relapsed [5]. Szczesny et al. identified anti-HMGCR antibodies in 13 of 312 patients with inflammatory myopathy, only 2 of whom had used a statin [6]. The CK in the present case exceeded the cohort means and the range reported in the recent multinational incidence cohort [7]. A prior case report likewise illustrates that anti-HMGCR testing should not be restricted to statin users [11].

Several non-statin factors have been proposed to account for anti-HMGCR antibody production in statin-

naïve patients such as ours but were not specifically investigated in this case. Genetic susceptibility is the most firmly established, with the HLA class II allele DRB1\*11:01 found to be present in roughly 70% of anti-HMGCR-positive patients compared with about 15% of the general population [12]. Dietary exposure to naturally occurring statins has been advanced to explain the lower rate of pharmaceutical statin exposure in Asian cohorts: red yeast rice contains monacolin K, which is chemically identical to lovastatin, and oyster mushrooms (approximately 2.7% lovastatin by dry weight), shiitake mushrooms, Pu-erh tea, and the herbal supplement *Bacopa monnieri* have all been implicated, with case reports describing disease triggered or exacerbated by mushroom ingestion [13]. Occult malignancy is a further consideration, although the data are conflicting: a cohort of 115 patients reported synchronous cancer in 11.5% of anti-HMGCR-positive patients, exceeding the expected population rate [14], whereas larger series found no excess cancer risk relative to matched controls, with advancing age the principal predictor [15]. Age-appropriate malignancy screening is of particular relevance in the present patient given his age and substantial unintentional weight loss. Finally, non-statin pharmacologic and environmental triggers, including immune checkpoint inhibitors, antiretrovirals, anti-tumor necrosis factor agents, interferons, and hydroxychloroquine, have been reported in necrotizing autoimmune myopathy [12]. In this patient, HLA typing, a dietary history for natural statin sources, and age-appropriate malignancy screening were not systematically pursued, which we acknowledge as a limitation.

Treatment data remain observational. Anti-HMGCR antibody levels correlate with CK and strength but may remain detectable despite improvement [16]. In a review encompassing 691 published patients, 84.9% received glucocorticoids and a median of 1.5 additional immunosuppressive agents [17]. In a 31-patient cohort, IVIG started within six months of diagnosis was associated with greater functional improvement; at 12 months, 7 patients in the delayed-treatment group still required a walker or wheelchair compared with none in the earlier-treatment group [18]. The present patient's early functional response is consistent with these observations, although a single case cannot establish treatment efficacy. His fluctuating CK during the prednisone taper also shows that functional recovery can precede biochemical normalization.

The serial biochemistry supports a substantial muscle contribution. AST and ALT declined after treatment, while alkaline phosphatase and bilirubin were not elevated and albumin was normal when measured. In an 85-patient inflammatory myopathy series, AST and ALT were elevated in 85% and 80%, respectively, and correlated strongly with CK [8]. Nathwani et al. also reported aminotransferase elevations in 16 patients with muscle necrosis and no evidence of liver disease [9]. In rhabdomyolysis, CK and aminotransferases may rise and fall together, whereas bilirubin, alkaline phosphatase, and gamma-glutamyl transferase are not expected to track isolated muscle injury [10]. In this patient, aminotransferases normalized months before CK, illustrating that their trajectories need not be identical.

The biopsy did not show a recognized pattern of anti-HMGCR disease. Hepatic HMGCR expression does not itself demonstrate antibody-mediated injury [1]. Lipofuscin has been documented in human liver biopsies and varies with age [19], while glycogenated nuclei occur in nonalcoholic fatty liver disease and other settings and are not specific for anti-HMGCR myopathy [20]. The anti-HMGCR cohorts reviewed here did not report a reproducible hepatic histopathologic pattern. The biopsy is therefore best treated as mild, nonspecific coincident pathology rather than evidence of direct hepatic autoimmunity; nonetheless, because these changes were interpreted as mild resolving liver injury, a concurrent hepatic contribution to the aminotransferase elevation cannot be definitively excluded.

A major limitation is the absence of serial gamma-glutamyl transferase (GGT) and international normalized ratio measurements. Because the central question is hepatic versus muscle origin of the aminotransferases, and GGT in particular is not expected to rise from skeletal muscle injury, serial GGT would have been the single most informative discriminator [10]; it was not obtained during the patient's course and cannot be added to Table 2. Bilirubin and albumin were within their reference intervals when measured but were not serially tracked. Additional limitations include the single-patient, retrospective design; nonuniform laboratory sampling; absence of electromyography and muscle biopsy; no systematic investigation of non-statin triggers (HLA typing, dietary natural statins, and malignancy screening); and no independent pathologist re-review. In patients with proximal weakness and elevated aminotransferases, CK should be checked early alongside liver evaluation. A concurrent hepatic process remains a concern when cholestatic markers, synthetic function, imaging, histology, or the enzyme trajectory cannot be explained by muscle injury.

## Conclusions

The clinical phenotype, severe hyperCKemia, anti-HMGCR seropositivity, magnetic resonance imaging findings, and longitudinal biochemical response favored a major skeletal muscle contribution to the aminotransferase elevation, although a concurrent mild hepatic process could not be definitively excluded, even when a liver biopsy shows mild nonspecific abnormalities. CK should be measured early in patients with proximal weakness and transaminitis, while evidence from cholestatic markers (including GGT), synthetic function, imaging, histology, and serial trends should guide evaluation for concurrent liver disease. Clinical recovery may precede biochemical recovery: this patient improved soon after immunotherapy, but CK did not normalize until approximately 18 months.

## Additional Information

### Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Abigail N. Horrar, John T. Meghreblian, Benjamin E. Jewett

**Acquisition, analysis, or interpretation of data:** Abigail N. Horrar, John T. Meghreblian, Benjamin E. Jewett

**Drafting of the manuscript:** Abigail N. Horrar, John T. Meghreblian, Benjamin E. Jewett

**Critical review of the manuscript for important intellectual content:** Abigail N. Horrar, John T. Meghreblian, Benjamin E. Jewett

**Supervision:** Benjamin E. Jewett

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