


CASE REPORT

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# Macrophage activation syndrome with acute hepatitis in a patient with adult-onset immunodeficiency with anti-interferon gamma antibodies: a case report

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## Abstract

**Background** Macrophage activation syndrome is a rare disorder leading to unregulated immune activity manifesting with nonspecific constitutional symptoms, laboratory abnormalities, and multiorgan involvement. We report the case of a patient who presented with acute hepatitis secondary to macrophage activation syndrome diagnosed by liver biopsy and successfully treated with intravenous immune globulin, anakinra, and rituximab.

**Case presentation** A 42-year-old Laotian woman with adult-onset immunodeficiency with anti-interferon gamma antibodies presented with a fever, headache, generalized myalgia, dark urine, and reduced appetite in the setting of family members at home with similar symptoms. Her laboratory workup was notable for evidence of acute hepatitis without acute liver failure. After an unrevealing comprehensive infectious and noninvasive rheumatologic workup was completed, a liver biopsy was performed ultimately revealing the diagnosis of macrophage activation syndrome. She was successfully treated with intravenous immune globulin, anakinra, and rituximab.

**Conclusion** This case highlights the importance of maintaining macrophage activation syndrome on the differential of a patient with acute hepatitis of unknown etiology in the correct clinical context and the value of a liver biopsy in making a diagnosis when noninvasive testing is unrevealing.

**Keywords** Macrophage activation syndrome, Adult-onset immunodeficiency with anti-interferon gamma antibodies, Acute hepatitis, Liver biopsy

## Background

Macrophage activation syndrome (MAS) is thought to be related to a defect in lymphocyte cytolytic activity responsible for maintaining appropriate level of immune response to tissue injury from infection or inflammation [1]. MAS can be a challenging diagnosis to make given its nonspecific clinical manifestations, most commonly featuring fever, hyperferritinemia, hypertriglyceridemia, pancytopenia, fibrinolytic consumptive coagulopathy, and hepatic dysfunction [1]. Several case reports have characterized various presentations of MAS with a common theme of underlying immunodeficiency secondary to an autoimmune condition triggered by a superimposed

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infection [2–7]. We report the case of a patient with adult-onset immunodeficiency with anti-interferon gamma antibodies who presented with acute hepatitis ultimately diagnosed with MAS through liver biopsy.

### Case presentation

Two months prior to admission to our hospital, a 42-year-old Laotian woman was hospitalized for an expedited workup of a constellation of symptoms, including progressive generalized musculoskeletal pain, persistent dry cough, weakness, generalized lymphadenopathy, and unintentional 20-pound weight loss. During that admission, she was diagnosed with disseminated *Mycobacterium hassicum* infection and started on a 6-month course of clarithromycin, imipenem/cilastatin, moxifloxacin, and ceftaroline. Because this opportunistic infection is typically seen in immunocompromised individuals, a workup to determine the underlying cause of her immunodeficient status was initiated and revealed adult-onset immunodeficiency with anti-interferon gamma antibodies.

Two months after initiation of her antibiotic regimen, the patient represented for evaluation of fever, headache, generalized myalgia, dark urine, and reduced appetite in the setting of family members at home with similar symptoms. Her vital signs were notable for fever to 102.9 °F and tachycardia. Initial laboratories were notable for a respiratory viral panel positive for human rhinovirus and a hepatic panel showing elevated aspartate aminotransferase (AST) 1281 U/L (ref <45 U/L), alanine aminotransferase (ALT) 511 U/L (ref <50 U/L), and alkaline phosphatase (ALP) 265 U/L (ref 40–150 U/L) (Table 1). The patient had no history of liver disease and liver function tests were normal as recently as 2 weeks prior to this admission. Her total bilirubin, direct bilirubin, and ammonia were within normal limits, and

international normalized ratio (INR) was elevated at 1.60 (ref 0.85–1.15). Viral hepatitis panel (including hepatitis A, B, C and HIV), abdominal ultrasound with Doppler, and autoimmune hepatitis serologies (including anti-smooth muscle, antinuclear, and antimitochondrial antibodies) were unrevealing.

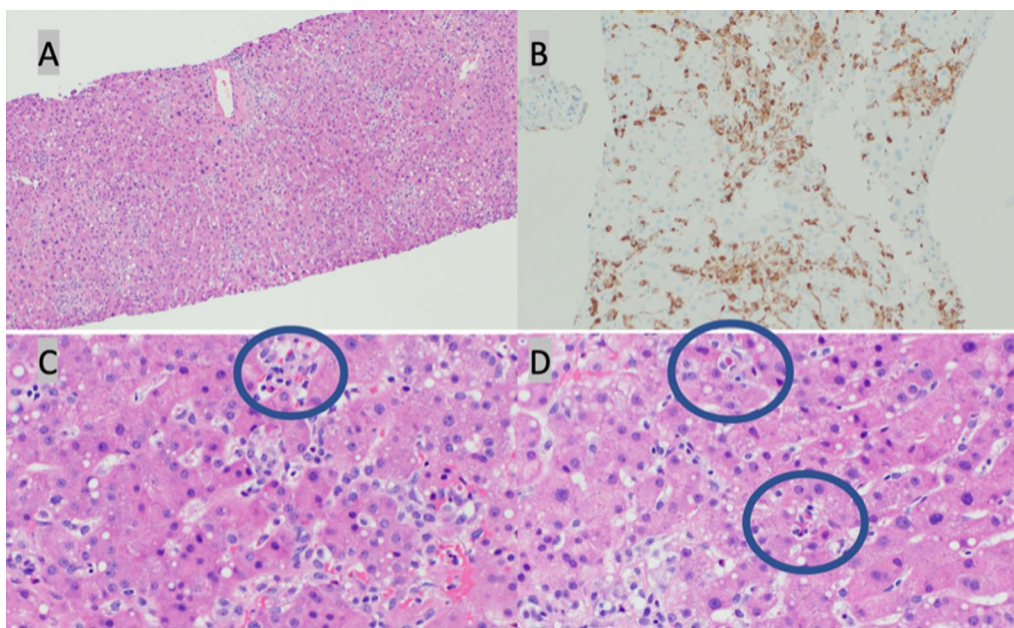
The patient's liver enzymes continued to rise over the next several days to AST 4188 U/L, ALT 684 U/L, and ALP 669 U/L with no corresponding decline in synthetic liver function. After consultation with infectious disease specialists, the patient's antibiotic regimen was held due to concern for possible acute hepatitis secondary to drug-induced liver injury. During this time, she remained intermittently febrile and developed a generalized tonic-clonic seizure. Subsequent nuchal rigidity prompted a lumbar puncture and empiric treatment for meningitis. A comprehensive rheumatologic and infectious disease workup had been unrevealing to this point. With new infections and malignancy essentially ruled out, work up for a dysregulated immune response was pursued, revealing a ferritin level of 62,225 ng/mL (ref 6–175 ng/mL), triglycerides 343 mg/dL (ref <150 mg/dL), white blood cell count 12,600/μL (ref 4000–11,000/μL), hemoglobin 8.4 g/dL (ref 11.7–15.7 g/dL), and platelet count 27,000/μL (ref 150,000–450,000/μL). Notably, a soluble interleukin (IL) 2 receptor alpha level resulted 6477 pg/mL (ref <2700 pg/mL).

A liver biopsy was obtained to better characterize the systemic process affecting the patient. The biopsy revealed prominent predominantly sinusoidal but also lobar and portal clusters of reactive Kupffer cells with consequent small foci of hepatocellular injury and necrosis (Fig. 1). Bile duct architecture was preserved and immunostains were negative for adenovirus, cytomegalovirus, acid fast bacilli, and Epstein–Barr virus. With

**Table 1** Notable laboratory values during hospitalization

	Patient's result day 1	Patient's result day 5	Patient's result day 14	Patient's result day 90	Reference range
Total bilirubin (TBili) mg/dL	1.2	1.3	0.7	0.9	0.2–1.3
Aspartate aminotransferase (AST) (U/L)	1281	4822	28	17	<45
Alanine aminotransferase (ALT) (U/L)	511	686	55	27	<50
Alkaline phosphatase (ALP) (U/L)	265	632	194	57	40–150
INR	1.60	1.31	1.18		0.85–1.15
Ferritin (ng/mL)		62,225	659	25	12–150
Triglycerides (ng/dL)		343			<150
C-reactive protein (mg/L)		16.2	<3.0	<3.0	<5
Hemoglobin (g/dL)	8.9	9.2	8.0	11.2	11.7–15.7
White blood count (10 <sup>3</sup> L)	5.3	20.3	5.8	3.6	4.0–11.0
Platelet count (10 <sup>3</sup> /μL)	101	123	192	236	150–450

AST Aspartate aminotransferase; ALT Alanine aminotransferase; ALP Alkaline phosphatase; INR International normalized ratio; CRP C-reactive protein



**Fig. 1** **A** Hematoxylin and eosin (H&E) 100 x: clusters of sinusoidal histiocytes. **B** CD68 stain, 200 x: clusters of sinusoidal histiocytes. **C** H&E 400 x: clusters of sinusoidal histiocytes with hemophagocytosis (circle). **D** H&E 400 x: clusters of sinusoidal histiocytes with hemophagocytosis (circles)

the patient's history of acquired immunodeficiency and clinical presentation, the liver biopsy findings supported a diagnosis of acute hepatitis secondary to dysregulated immune response to rhinovirus infection leading to MAS. Treatment with intravenous immune globulin (IVIG), anakinra, and rituximab was initiated by consultants from hematology and rheumatology with subsequent improvement in clinical status, liver function tests, platelet count, and ferritin. Liver function tests improved within 2 weeks and normalized within 3 months. At most recent follow-up, the patient reported feeling well with resolution of presenting symptoms and normalization in inflammatory markers.

### Discussion and conclusion

This case presents an opportunity to explore a rare diagnosis of MAS presenting as acute hepatitis in a patient with a rare underlying etiology of immunodeficiency. Our patient was diagnosed with acquired immunodeficiency with anti-interferon gamma autoantibodies during her workup for nontuberculous mycobacterial infection prior to her presentation at our hospital. Acquired immunodeficiency with anti-interferon gamma autoantibodies is characterized by profound immunodeficiency with poor response to appropriate therapy for recurrent opportunistic infections [8]. Anti-interferon autoantibodies have previously been described to be frequently detected in Asian adults presenting with multiple opportunistic infections [9]. The cause of the development in these

autoantibodies remains unknown; however, it is suspected to be related to incompletely understood genetic factors [8]. While MAS is seen in the context of autoimmunity, we are unaware of any previously described cases of the development of MAS in a patient with acquired immunodeficiency with anti-interferon gamma autoantibodies [10].

There is a significant overlap between the presence of autoimmune and autoinflammatory diseases and the development of MAS [11]. This is notable given our patient's history of immunodeficiency secondary to acquired anti-interferon gamma antibodies. This underlying immunodeficiency likely served as the catalyst for a dysregulated immune response to an otherwise uneventful rhinovirus infection. There are several known etiologies of MAS, including triggers such as infection, inflammation, and malignancy. These triggers can lead to dysregulated activation of IL-1 and IL-18 pathways [10]. The pathophysiology of local hepatic tissue inflammation and destruction secondary to Kupffer cell activation has been previously well-described [12]. One case series of pediatric patients with MAS demonstrated liver biopsies with interferon gamma (IFN- $\gamma$ ) expression by CD8<sup>+</sup> lymphocytes and IL-6 and tumor necrosis factor alpha (TNF- $\alpha$ ) expression by hemophagocytosing macrophages [13]. These findings support the rationale behind the treatment strategy implemented for our patient including IVIG and the IL-1 receptor antagonist, anakinra. In general, treatment for MAS typically combines some form

of IL-1 suppression, corticosteroids, and the calcineurin inhibitor, cyclosporine [14]. Without early diagnosis and intervention, MAS has a high fatality rate [15].

Even with several prototypical features of MAS present in our patient, the diagnosis of MAS was elusive until a thoroughly negative infectious and noninvasive rheumatologic workup had been completed and the diagnosis not clinched until the results of the liver biopsy returned. A recent review demonstrated that liver biopsy successfully leads to a specific diagnosis in 84% of patients with persistently abnormal liver enzymes of unclear etiology [16]. Noninvasive imaging has recently increased in popularity owing to its accessibility and cost benefits, while competence in liver biopsy is no longer a requirement for advanced hepatology trainees [17]. However, liver biopsy remains irreplaceable in the diagnosis of infiltrative diseases and can offer a definitive diagnosis when the etiology of abnormal liver enzyme levels is unknown [18, 19]. In cases where understanding the etiology of acute hepatitis will ultimately guide disease course-modifying, and potentially life-saving, therapy, the benefits of liver biopsy far outweigh the associated risks; a recent review quantified the overall rate of bleeding after image-guided liver biopsy as 2% [20].

In summary, MAS is an inflammatory condition characterized by fever, lymphadenopathy, hepatosplenomegaly, pancytopenia, coagulopathy, and multiorgan involvement. This case highlights the importance of maintaining MAS on the differential diagnosis when considering a patient with the above constellation of symptoms, laboratory results, and physical exam findings. It also highlights the value of a liver biopsy in confirming the diagnosis and guiding targeted therapy in the setting of hepatic involvement.

#### Abbreviations

MAS	Macrophage activation syndrome
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
INR	International normalized ratio
TBili	Total bilirubin
IL	Interleukin
IVIG	Intravenous immune globulin
TNF- $\alpha$	Tumor necrosis factor alpha
IFN- $\gamma$	Interferon gamma

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Not applicable.

#### Author contributions

WH was responsible for drafting of the manuscript and data collection. BM critically reviewed and edited all aspects of the manuscript. OA performed analysis of the liver biopsy and provided the images included above. NL was responsible for drafting portions of the manuscript and critically reviewing and editing all aspects of the manuscript.

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#### Availability of data and materials

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#### Declarations

##### Ethics approval and consent to participate

Approval is not needed by the local Ethics Committee for case reports.

##### Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

##### Completing interests

Not applicable.

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