HHS Public Access

Author manuscript

Lancet Haematol. Author manuscript; available in PMC 2022 November 01.

Published in final edited form as:

Lancet Haematol. 2022 July ; 9(7): e546. doi:10.1016/S2352-3026(22)00037-0.

Idiopathic multicentric Castleman disease with arteriolar endotheliopathy and secondary hemophagocytosis

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Keywords

Castleman disease; TAFRO; anakinra; mesenteritis; hemophagocytic

The authors have written permission from the patient to submit this clinical picture for publication

A 46-year-old male presented to Vancouver General Hospital September 2021 with abdominal pain and fever. Physical exam revealed ascites, and dependent edema. Bloodwork demonstrated leukocytosis 31.5 × 10^9/L, (< 11), creatinine 191 μmol/L (<115), and alkaline phosphatase 262 U/L (<135), with normal transaminases. Computerized tomography scan showed hepatomegaly (21 cm), splenomegaly (15.5 cm), ascites, bilateral pleural effusions and soft tissue stranding within the omentum and mesentery with mildly enlarged cervical (1.2 cm) and mesenteric (1.3 cm) lymph nodes. He became thrombocytopenic 49 × 10^9/L (150–400), with elevated D-dimer of 38,533 μg/L (< 500), C-reactive protein 498 mg/L (< 3.1), interleukin (IL)-6 52.9 pg/mL (< 7), ferritin 1211 μg/L (< 300) and soluble interleukin-2 receptor alpha (IL2RA) 1556 U/mL (< 846). Serum protein electrophoresis was normal and IgG was 9.8 g/L (6.7–15.2). Autoimmune and infectious workup was negative, including ANA, ANCA, HIV, HHV-8 and COVID-19.

A core liver biopsy showed Kupffer cell hypertrophy with hemophagocytosis (figure). A minority of portal tracts were mildly inflamed, without interface activity, significant

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Contributors: We were all involved in caring for the patient. CMC and LYCC drafted the manuscript. DO provided the Figure and pathology expertise. We all edited and approved the final manuscript. The patient provided written consent for publication of the case.

Declaration of interests: We declare no competing interests.

bile duct injury or lobular inflammation. The hepatic arteriolar endothelium in several portal tracts contained reactive changes, including rarefied endothelial cell cytoplasm, with nuclear enlargement and rounding (figure). Hepatic venous and sinusoidal endothelia were unremarkable. There was no evidence of hepatic venous outflow impairment, fibrosis, or steatosis. Cervical lymph node biopsy revealed polyclonal plasmacytosis, increased vascularity and regressed germinal centers, compatible with idiopathic multicentric Castleman Disease (iMCD) (appendix). Bone marrow biopsy showed mild reticulin fibrosis and hemophagocytosis.

Given the constellation of thrombocytopenia, anasarca, reticulin fibrosis in the bone marrow, renal dysfunction, and organomegaly, the patient was diagnosed with iMCD-TAFRO. He was treated with anakinra 100 mg subcutaneously daily for 10 days followed by siltuximab 11 mg/kg intravenously every three weeks sirolimus 4 mg po daily and rituximab 375 mg/m2 intravenously weekly for four doses with excellent clinical response.

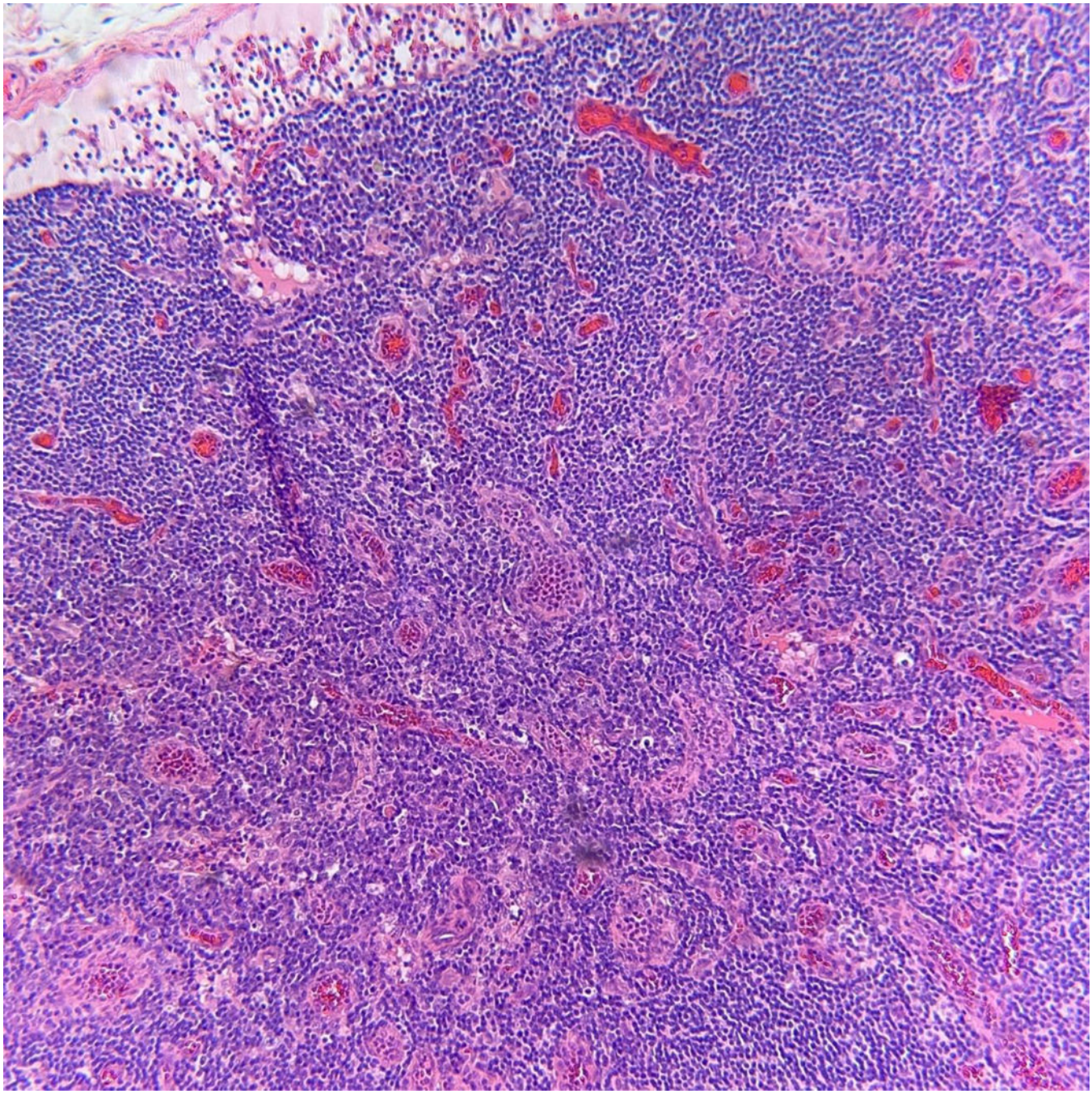
TAFRO is an aggressive cytokine storm disorder. Hemophagocytic lymphohistiocytosis is often considered in the differential, as both conditions can present with hemophagocytosis, severe inflammation and rapid deterioration. However, iMCD-TAFRO patients display markedly elevated CRP, and D-dimer with mildly elevated ferritin and IL2RA. Vascular changes have been reported in renal biopsies of iMCD-TAFRO. The hepatic endothelial changes in this case have not been previously reported and may be a useful clue for this elusive diagnosis.

Acknowledgements:

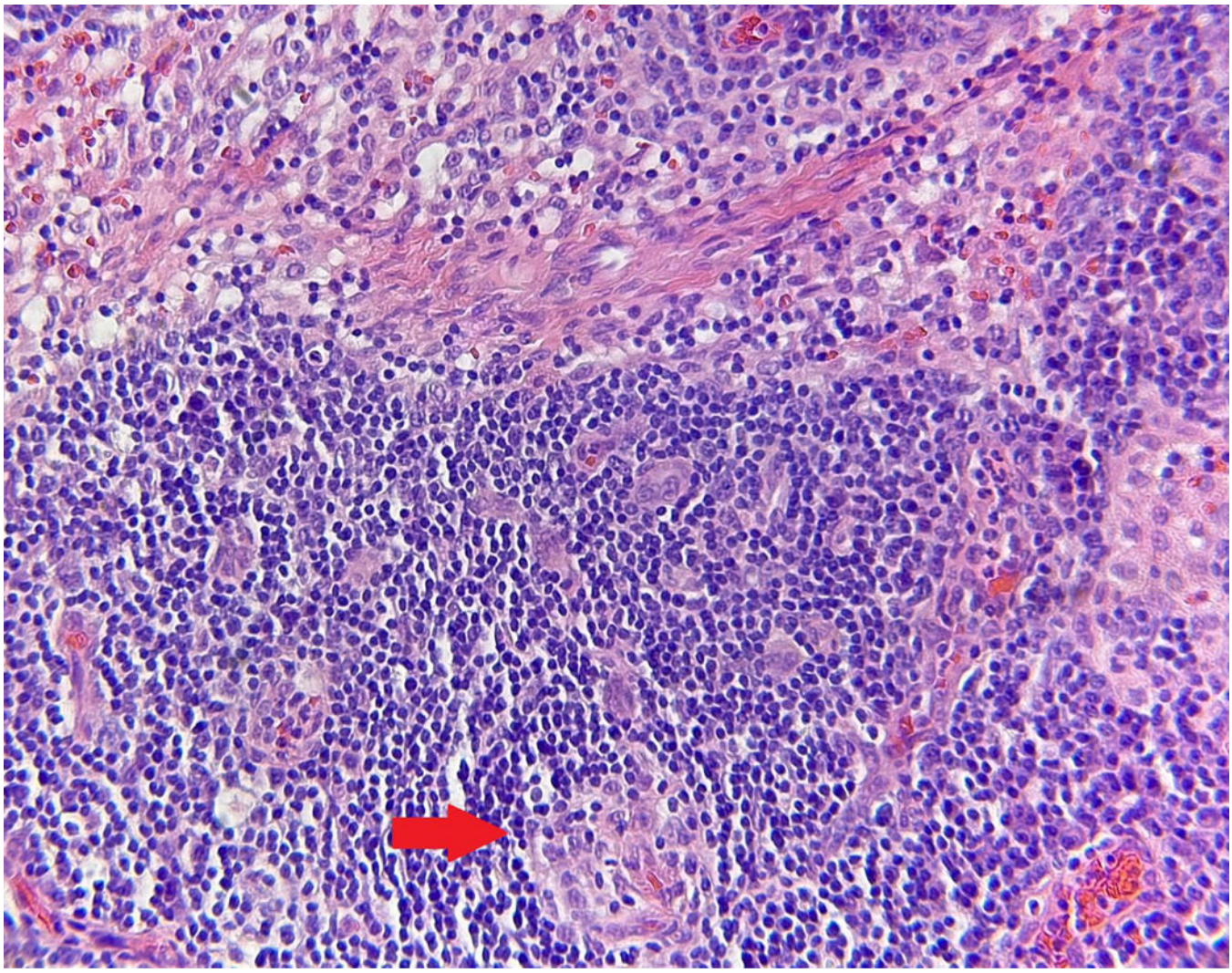
Luke Chen’s research is supported by the Hsu & Taylor Family

APPENDIX

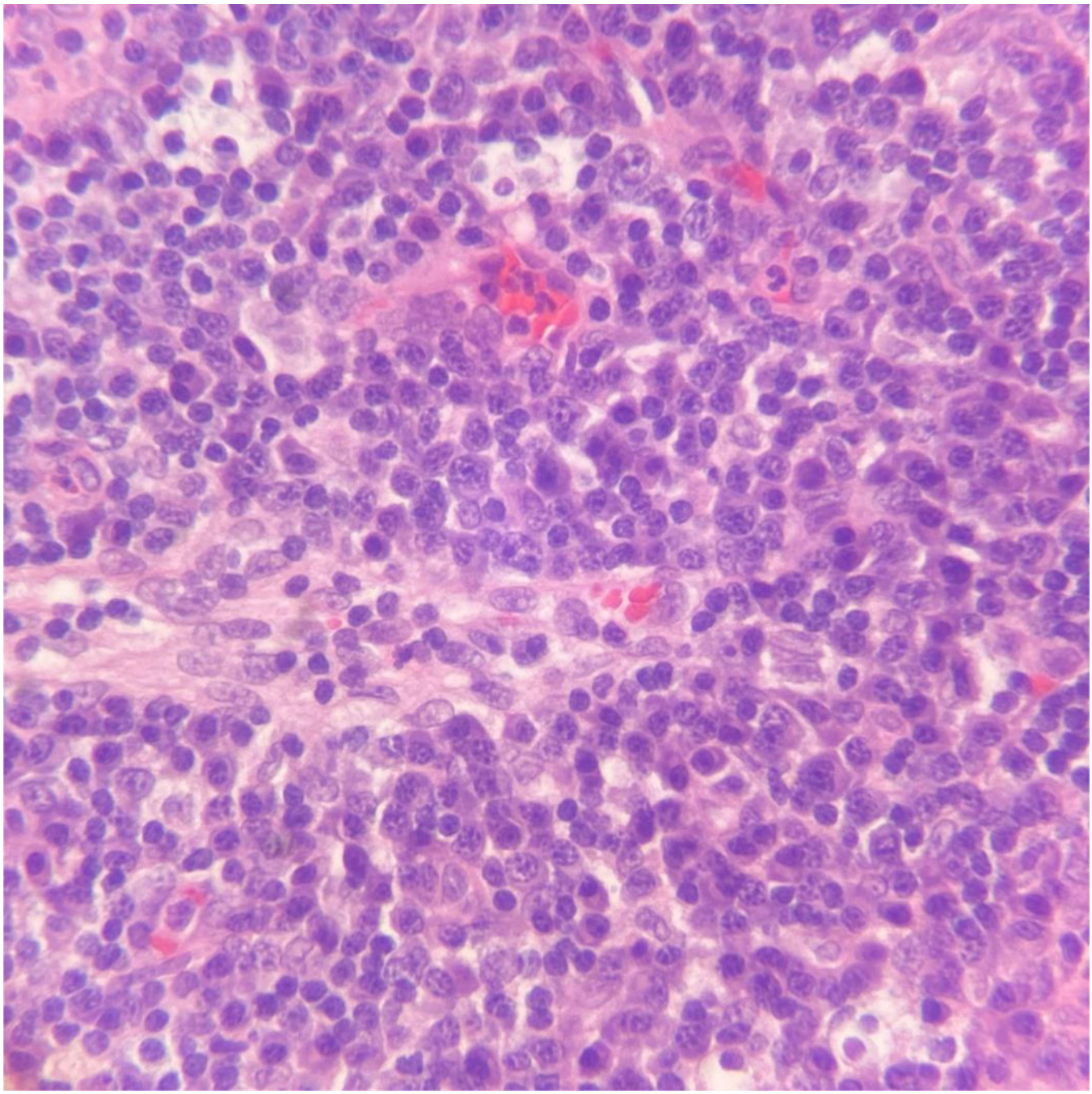
Appendix: Excisional lymph node biopsy



Excisional biopsy of cervical lymph node showing increased vascularity and polyclonal plasmacytosis. The histologic findings are in keeping with idiopathic multicentric Castleman disease. H&E, original magnification 100X.



Excisional biopsy of cervical lymph node showing regressed germinal center (red arrow). H&E, original magnification 200X.



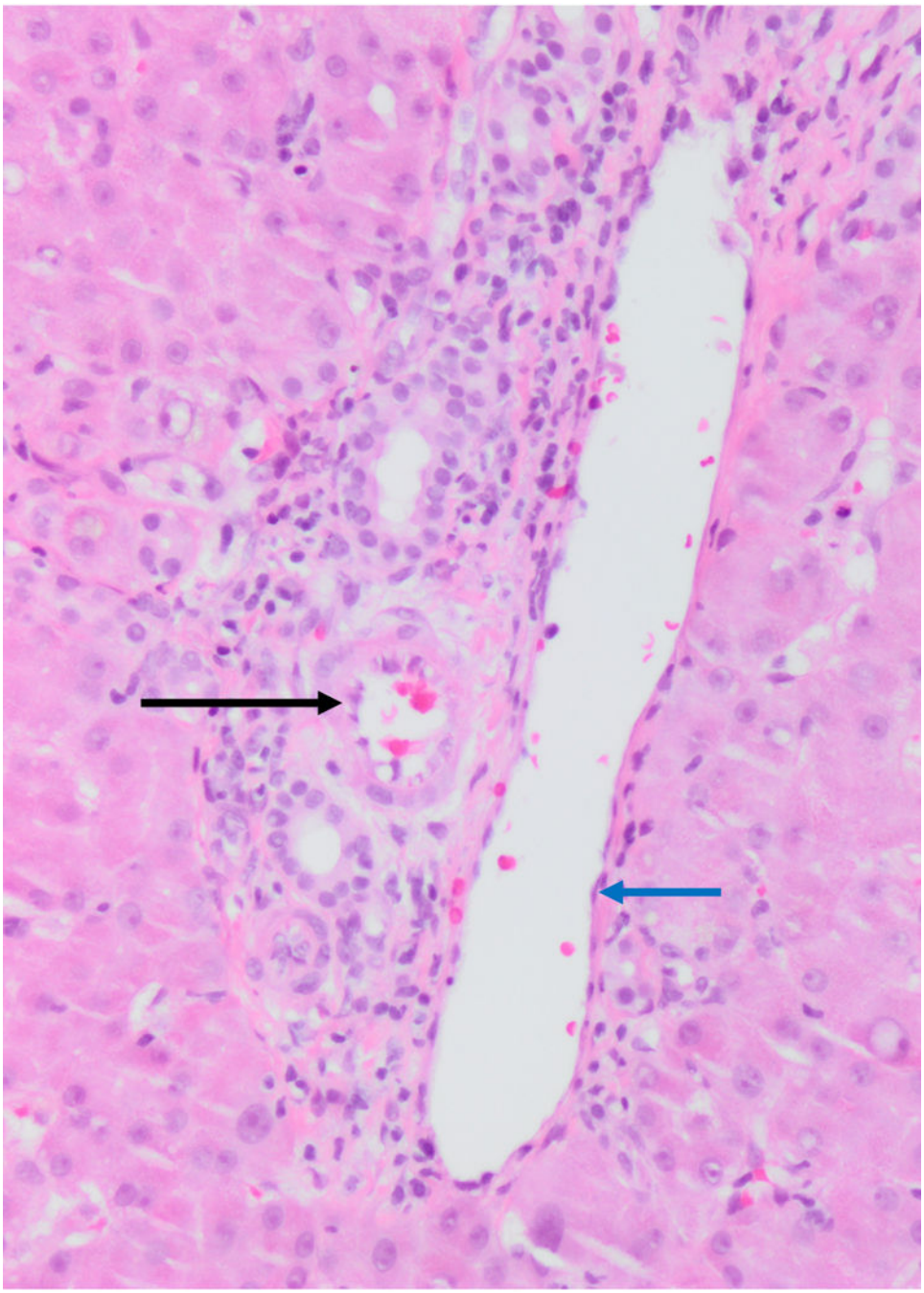
Excisional biopsy of cervical lymph node showing polyclonal plasmacytosis. H&E, original magnification 400X.

Clinical Question:

A 46-year-old male presented with two weeks of abdominal pain and fever. Physical exam was remarkable for anasarca, with bilateral pleural effusions, ascites, and dependent edema. Lab investigations revealed thrombocytopenia, cholestatic liver enzyme elevation, renal dysfunction and markedly elevated inflammatory markers (C-reactive protein 498 mg/L, ferritin 1211 μg/L, soluble interleukin-2 receptor alpha 1556 U/mL, interleukin-6 52.9 pg/mL, D-dimer 38,533 μg/L. Computed tomography showed lymphadenopathy up to 1.3 cm in the cervical chains and hepatosplenomegaly. Liver biopsy showed prominent hemophagocytosis and very reactive arterial endothelial cells. Which statement is correct?

1. The most likely diagnosis is intravascular lymphoma and the patients should undergo a bone marrow biopsy to confirm this
2. The most likely diagnosis is hemophagocytic lymphohistiocytosis and the patient should undergo a bone marrow biopsy to confirm this
3. The most likely diagnosis is metastatic adenocarcinoma and the patient should undergo upper and lower gastrointestinal endoscopy to confirm this
4. The most likely diagnosis is idiopathic multicentric Castleman disease, TAFRO subtype, and the patient should undergo an excisional lymph node biopsy to confirm this

Answer: 4)



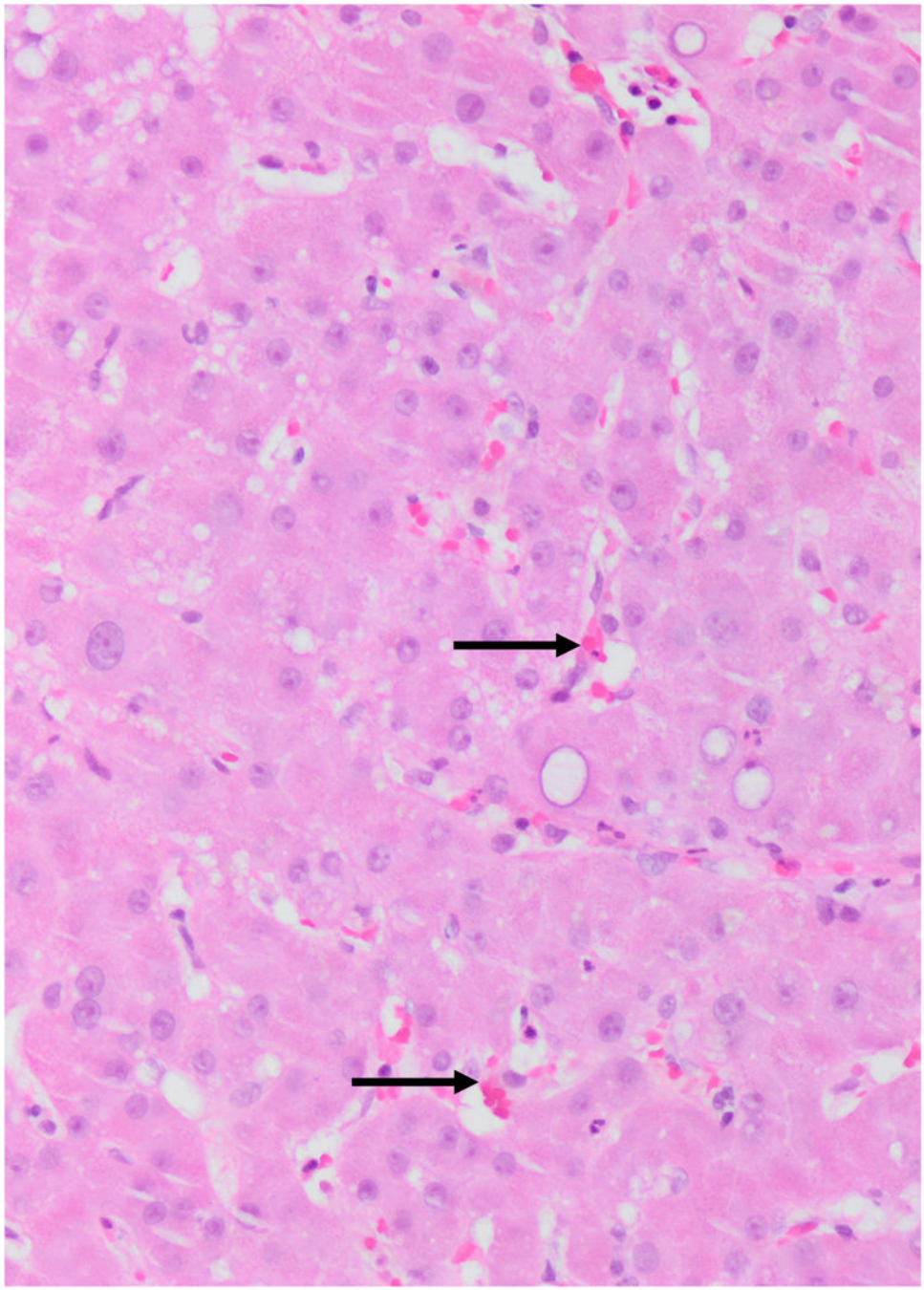


Figure: Liver biopsy demonstrating reactive arteriolar endothelium in TAFRO and reactive hemophagocytosis.

The portal tracts (A) contain reactive arteriolar endothelium (black arrows) and normal portal vein endothelium (blue arrow). H&E, original magnification 400X.Core needle biopsy of liver showing reactive hemophagocytosis by sinusoidal Kupffer cells (B).