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Idiopathic multicentric Castleman - TAFRO syndrome can mimic sepsis and myeloid neoplasia

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Castleman disease (CD), first described in the 1950s, is a heterogeneous lymphoproliferative disorder clinically categorized as unicentric (UCD) or multicentric (MCD) (Castleman 1954). Contemporary clinically oriented frameworks emphasize that management and prognosis are guided primarily by clinical context and recognize additional categories such as oligocentric CD and asymptomatic MCD, while subdividing MCD into HHV-8/KSHV-associated MCD, POEMS-associated MCD, and idiopathic MCD (iMCD), with clinical phenotypes including iMCD-TAFRO, iMCD-idiopathic plasmacytic lymphadenopathy (iMCD-IPL), and iMCD-NOS (Chen 2026). The main variants of Castleman disease have been incorporated into the most recent WHO-classification of lymphoid neoplasms (Zitat Alaggio et al.). TAFRO syndrome refers to the constellation of thrombocytopenia, anasarca, fever/marked inflammation, reticulin fibrosis/renal dysfunction, and organomegaly and can occur in association with iMCD (iMCD-TAFRO), but importantly it may also present without lymphadenopathy, making a diagnosis of CD impossible by definition and often limiting access to diagnostic lymph node histopathology (Otsuka 2025). Clinically, TAFRO frequently presents as a fulminant, sepsis-like hyperinflammatory syndrome and may overlap with hematologic malignancy-associated findings, creating substantial diagnostic pressure toward infectious or myeloid neoplastic etiologies (Fajgenbaum 2017, Nishimura 2021). In the present case, generalized lymphadenopathy enabled biopsy support for iMCD-TAFRO, yet the presentation mimicked fulminant sepsis with multiorgan failure and marrow findings suggestive of a myeloid neoplasm – illustrating key pitfalls and the need for a multidisciplinary, clinicopathologic approach to timely immunomodulatory therapy.

Because of its hyperinflammatory presentation, iMCD-TAFRO can closely resemble sepsis, and infections may also complicate the course under treatment. Here, we highlight two underappreciated pitfalls: procalcitonin can exceed 100 ng/mL in iMCD-TAFRO, and bone marrow (BM) findings may strongly mimic a myeloid neoplasm, yet both may rapidly resolve with IL-6-directed therapy.

A previously healthy 20-year-old woman of Ghanaian origin was transferred to our ICU with high fever, abdominal pain, severe thrombocytopenia, acute kidney injury with a tubular proteinuria, and a markedly inflammatory laboratory profile (Table 1). A sepsis-like condition rapidly developed, with a SOFA score of up to 16 points, requiring invasive ventilation, need of dialysis, and high-dose catecholamine.

A comprehensive infectious work-up was initiated promptly. Contrast-enhanced CT showed polyserositis, generalized lymphadenopathy, hepatosplenomegaly, and pneumonic infiltrates (Figure 1). Blood and urine cultures remained negative. Bronchoscopy with lavage, pleural and ascites taps, and a lymph-node biopsy revealed inflammatory changes without organisms. Broad eubacterial, panfungal, and mycobacterial PCRs were negative. Given a recent vacation in southern Germany, leishmaniasis was excluded. Despite broad anti-infective therapy – ceftriaxone, meropenem, levofloxacin, piperacillin/tazobactam – infection markers did not improve. The patient required intubation and high-dose vasopressor support.

Pericardial fluid aspiration showed hemorrhagic cytology with presumed myeloid precursor cells. Microbiology was negative. This was followed by BM aspiration and biopsy. Histopathology showed 100% cellularity with architectural disturbance, extensive atypical megakaryocytic proliferation, and myelofibrosis grade 1 with open sinusoids (Figure 2 A-C). Mild increases in plasma cells and mature T cells were present (approximately CD4:CD8 = 1:1). Assays for Leishmania and EBV were negative. Overall, the marrow findings were strongly suggestive of a myeloid neoplasia

with mild myelofibrosis. Targeted Illumina Myeloid NGS and FISH for TP53 alterations revealed no pathogenic mutations or fusions. Whole genome sequencing (WES) from blood was unremarkable. Core biopsy of an axillary lymph node showed lymphadenitis with a marked increase of polytypic plasma cells (Figure 2 D-F). EBER in situ hybridization and HHV8 were negative. There were no indications of IgG4 proliferation (<100 IgG4-positive plasma cells/mm2). One major histopathological criterium for the diagnosis of HHV8-negative-iMCD was fulfilled with a grade 3 plasmocytosis (sheet-like polytypic plasmacytosis) in the interfollicular space. (Fig. 2E-F; Fajgenbaum 2017). In addition, regressive B-cell follicles were observed in line with the histological criteria of TAFRO-iMCD (Iwaki 2016). Although preferred, lymph node extirpation could not be performed in the acute phase due to hemodynamic and hemostatic reason. Flow cytometry failed to detect any malignant cells in either the pericardial effusion or the blood. PNH was ruled out by FACS analysis.

Multidisciplinary rounds including infectious diseases, hematology, oncology, rheumatology, nephrology, and intensive care continued the exclusion work-up. Duodenal, colonic, and skin biopsies showed no malignancy or infection, including Whipple disease. Additional blood PCRs testing for histoplasmosis and parvovirus were negative. Immunofixation and broad autoimmunity testing were unremarkable. There was no evidence of thrombotic microangiopathy: normal ADAMTS-13 activity, Shiga toxin negative, no schistocytes.

Based on the presence of the TAFRO clinical constellation together with Castleman disease-compatible lymph node histopathology – and negative testing for relevant mimickers, including HHV-8 –, we made the diagnosis of biopsy-supported iMCD-TAFRO. Major alternative diagnoses such as bacterial sepsis, HLH/MAS, autoimmune disease, lymphoma, and other hematologic malignancies were systematically excluded (Chen 2025).

In view of the persistently very high procalcitonin levels, we decided against the use of steroids and opted for intensified IL-6 blockade. The patient (body weight 70 kg) received siltuximab 11 mg/kg (770 mg) once, followed by tocilizumab 8 mg/kg (560 mg) on 3 consecutive days as a short rescue strategy. This resulted in rapid clinical improvement: fevers resolved, thrombocytopenia corrected, and procalcitonin normalized. She was weaned from the ventilator and dialysis and was ambulatory on the ward within two weeks. The clinical course, together with the absence of myeloid driver alterations, argued against an underlying myeloid neoplasm; in clinicopathologic correlation, the megakaryocytic proliferation and reticulin fibrosis were deemed reactive in the context of TAFRO (Belyaeva 2022). She was discharged on siltuximab q3 weeks. At last follow-up she remains in sustained remission with normal platelets/inflammatory markers and normal renal function. There is no longer any evidence of serositis.

Idiopathic multicentric Castleman disease (iMCD) is a cytokine-driven lymphoproliferative disorder characterized by systemic inflammation with multiorgan dysfunction; iMCD includes iMCD-TAFRO and iMCD-NOS as clinical subtypes in WHO-HAEM5 (Alaggio 2022). In WHO-HAEM5, iMCD-TAFRO is defined by five required clinical features – thrombocytopenia, anasarca, fever/marked inflammation, renal dysfunction or BM reticulin fibrosis, and organomegaly – alongside iMCD lymph-node histology and appropriate exclusions (Alaggio 2022, Nishimura 2021, Fajgenbaum 2017). This framework differentiates iMCD-TAFRO from iMCD-NOS, which more often shows thrombocytosis and hypergammaglobulinemia (Alaggio 2022, Iwaki 2016).

Clinically, our patient had T: severe thrombocytopenia ($4\times10^3/\mu L$), A: polyserositis/anasarca, F:

hyperinflammation (fever; CRP 526 mg/L; IL-6 504 pg/mL), R: dialysis-requiring renal failure, and O: hepatosplenomegaly with generalized lymphadenopathy, fulfilling all five TAFRO features. Lymph node histology and broad exclusions met iMCD essential criteria (Alaggio 2022, Fajgenbaum 2017, Nishimura 2021). Applying the 2019 updated TAFRO severity score, she reaches 12/12 (grade 5, "very severe"). Note that typical histopathology described for TAFRO lymph nodes is a combination of atrophic follicles with prominent interfollicular vascular proliferation and fewer interfollicular plasma cells compared to iMCD-NOS – important nuance given our node demonstrated atrophic B-follicles and an increase in interfollicular plasma-cells- still compatible with iMCD by consensus criteria (Alaggio 2022, Iwaki 2016).

The sepsis phenotype (SOFA domains: thrombocytopenia, renal failure, vasopressor need) is common in iMCD-TAFRO flares, driving empiric broad-spectrum antimicrobials (Singer 2016). A key pitfall is procalcitonin (PCT). Although widely used as a biomarker of bacterial infection, PCT can be markedly elevated in cytokine-storm biology. Elevated PCT has been reported in iMCD-TAFRO (Nara 2017), and a prior case of HHV8-associated MCD described PCT >100 ng/mL (Bissinger 2010). Together with our patient's PCT >100 ng/mL despite repeatedly negative microbiology, these observations emphasize that extreme PCT elevations do not exclude Castleman-spectrum hyperinflammation and highlight the need for improved biomarker-based differentiation across cytokine-storm syndromes (e.g., TAFRO/HLH vs sepsis). Thus, PCT-guided 'bacterial sepsis' algorithms may be misleading in cytokine-driven hyperinflammation, and persistently negative microbiology should prompt consideration of iMCD-TAFRO even at extreme PCT levels.

Another key mimic in fulminant cytokine-storm presentations is secondary HLH/MAS. Recent data suggest that readily available inflammatory markers can support early differentiation: sCD25 and ferritin are typically substantially higher in HLH, whereas CRP tends to be higher in iMCD-TAFRO, providing a practical biomarker pattern to guide diagnostic prioritization when microbiology is negative and clinical overlap is pronounced (Rowe 2025).

BM in iMCD-TAFRO often shows hypercellularity, megakaryocytic hyperplasia, and reticulin fibrosis, which can mimic MPN/MDS (Belyaeva 2022, Alaggio 2022, Iwaki 2016). In our case, 100% cellularity with atypical megakaryocytes and MF-1 prompted suspicion of a myeloid neoplasm. However, NGS/FISH were negative, lymph-node and clinical features supported iMCD, and rapid response to IL-6 blockade argued for reactive changes rather than clonal myeloid disease. Awareness of this mimicry is crucial to prevent misdiagnosis and inappropriate cytotoxic therapy (Belyaeva 2022, Alaggio 2022).

International guidelines recommend anti-IL-6 therapy – siltuximab first-line, tocilizumab when siltuximab is unavailable – with steroids as needed in severe cases. Our patient's intensified IL-6 blockade led to reversal of organ failure, consistent with the IL-6-driven biology recognized by WHO and consensus frameworks (van Rhee 2020, Pierson 2023).

In fulminant sepsis-like presentations with persistently negative microbiology, iMCD-TAFRO should be considered – even when procalcitonine is extremely high – and IL-6 blockade instituted promptly when diagnostic criteria are met.

In summary, it must be emphasized that clinicians need to be very aware of the entity of TAFRO syndrome. This is due to its acute, often life-threatening course with multi-organ failure and to the extremely relevant differential diagnoses. Particularly in the setting of intensive care for critically

ill patients, the almost perfect imitations of myeloproliferative neoplasia (cytopenias, fibrosis in BM, splenomegaly) and sepsis (high PCT values, inflammation, cytokine storm) can mean diametrically different therapeutic approaches. This can sometimes significantly delay the actual diagnosis and the targeted therapy.

Patient informed consent for publication was obtained. The report respects the ethical rules of our country.

Abbreviations:

ADAMTS-13: A disintegrin and metalloproteinase with thrombospondin motifs-13; BM: bone marrow; CD: Castleman disease; CRP: C-reactive protein; CT: Computed tomography; EBER: Epstein–Barr virus–encoded small RNAs; EBV: Epstein–Barr virus; FACS: Fluorescence-Activated Cell Sorting; FISH: Fluorescence in situ hybridization; HHV8: Human herpesvirus 8; ICU: Intensive care unit; IL-6: Interleukin-6; iMCD: Idiopathic multicentric Castleman disease; iMCD-NOS: Idiopathic multicentric Castleman disease, not otherwise specified; iMCD-TAFRO: Idiopathic multicentric Castleman disease, TAFRO subtype (Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis/Renal insufficiency, Organomegaly); KSHV: Kaposi sarcoma–associated herpesvirus (HHV8); MCD: Multicentric Castleman disease; MF-1: Myelofibrosis grade 1; MPN/MDS: Myeloproliferative neoplasm / Myelodysplastic syndrome; NGS: Next-generation sequencing; NOS: Not otherwise specified; PCR: Polymerase chain reaction; PCT: Procalcitonin; PNH: paroxysmal nocturnal hemoglobinuria; SOFA: Sepsis-related Organ Failure Assessment; TAFRO: Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis/Renal insufficiency, Organomegaly; TP53: Tumor protein p53; UCD: Unicentric Castleman disease; WES: Whole-exome sequencing; WHO: World Health Organization; WHO-HAEM5: WHO 5th edition classification of haematolymphoid tumours.

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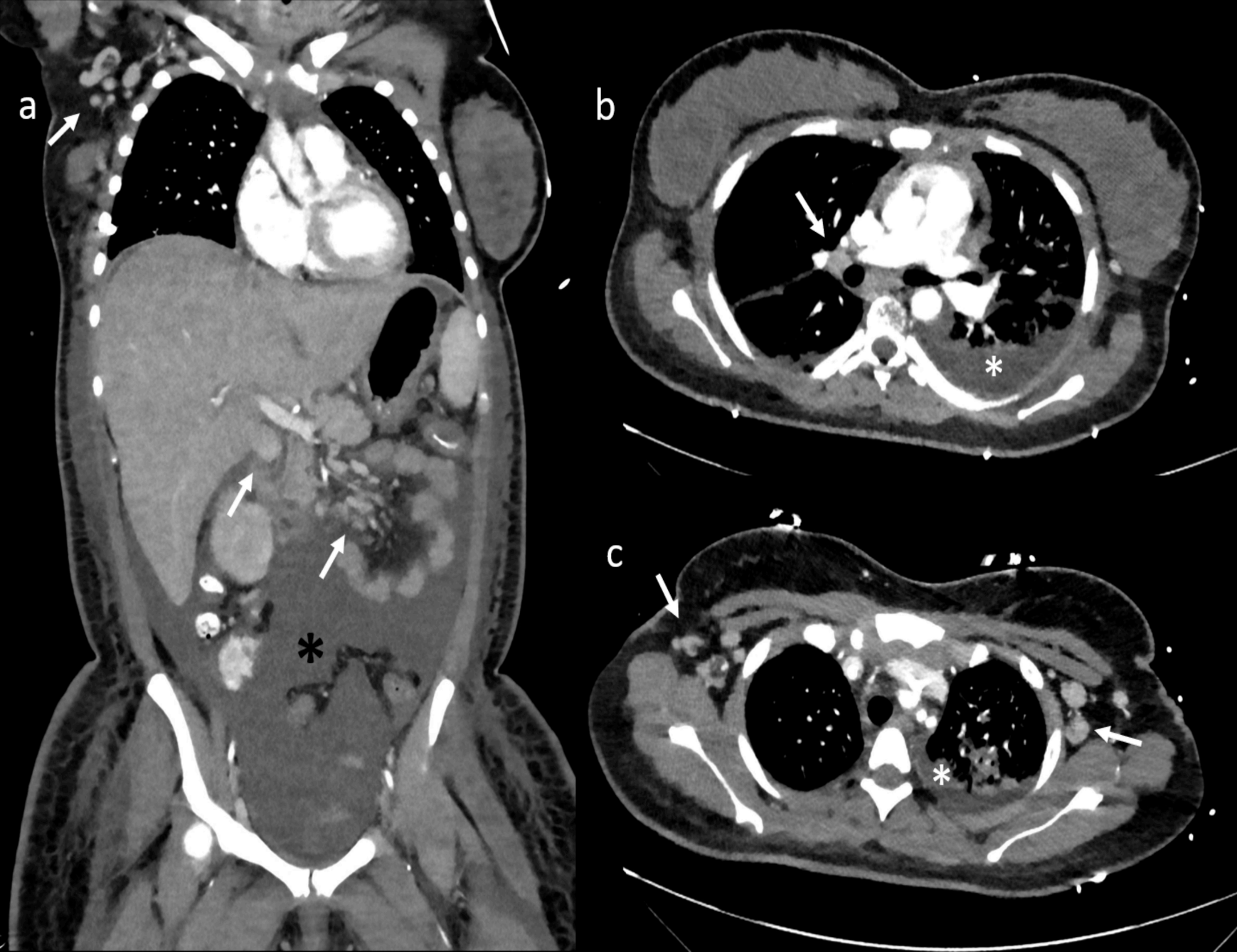
Value	Reference	Baseline	After treatment
hemoglobin (g/dl)	12.0-15.4	6.9	10.4
platelets ($\times 10^9$/l)	150-370	6	221
C-reactive proteine (mg/l)	<5,0	526	<0,6
sCD25 (kU/l)	<623	4201	-
ferritin (µg/l)	9-140	1813	149
procalcitonine (µg/l)	≤0.05	>100	0.06
creatinine (µmol/l)	45-84	280	55.3
serum albumin (g/l)	35-53	19.2	46.7
urin albumin (mg/g Krea)	<20	59.8	3.78
serum Immunoglo-bulin G (g/l)	7-16	11	8.8
immunofixation	Negative	negative	

Table 1. Laboratory values. Shown are clinical chemistry parameters with reference, baseline value, and post-treament value.

Figure 1. **Contrast-enhanced computed tomography scan taken during the patient's stay in the intensive care unit, showing coronal and axial views with findings typical of TAFRO syndrome**. **A:** Marked hepatomegaly (25 x 17 x 23 cm), extensive ascites (black asterisk) and mesenteric, periportal and axillary lymphadenopathy with lymph nodes up to 16 mm short axis diameter (white arrows) are illustrated. **B:** Shows pleural effusions on the left side (white asterisk); as well as further lymphadenopathy on the right hilum (white arrow). **C:** Demonstrates the axillary lymphadenopathy (white arrows) as well as the right sides pleural effusion (white asterisk). Right sided pleural effusion was drained before CT.

Figure 2. Histopathology of the trephine biopsy and core biopsy of the lymph node, showing specific changes associated with iMCD/TAFRO at the time of diagnosis. A: Hematoxylin&Eosin (HE) stain with 40x magnification showing hypercellular bone marrow (BM) in trephine biopsy; **B:** HE stain with 400x magnification with hyperplastic haematopoesis; **C:** additional CD61 staining with 400x magnification pointing at groups and clusters of atypical megakaryocytes
D: HE staining of the lymph node core biopsy with 40x showing interfollicular expansion of polytypic plasma cells; E: additional kappa-in situ hybridization in 100x magnification and F: additional lambda-in situ hybridization in 100x magnification to demonstrate polytopic light-chain expression.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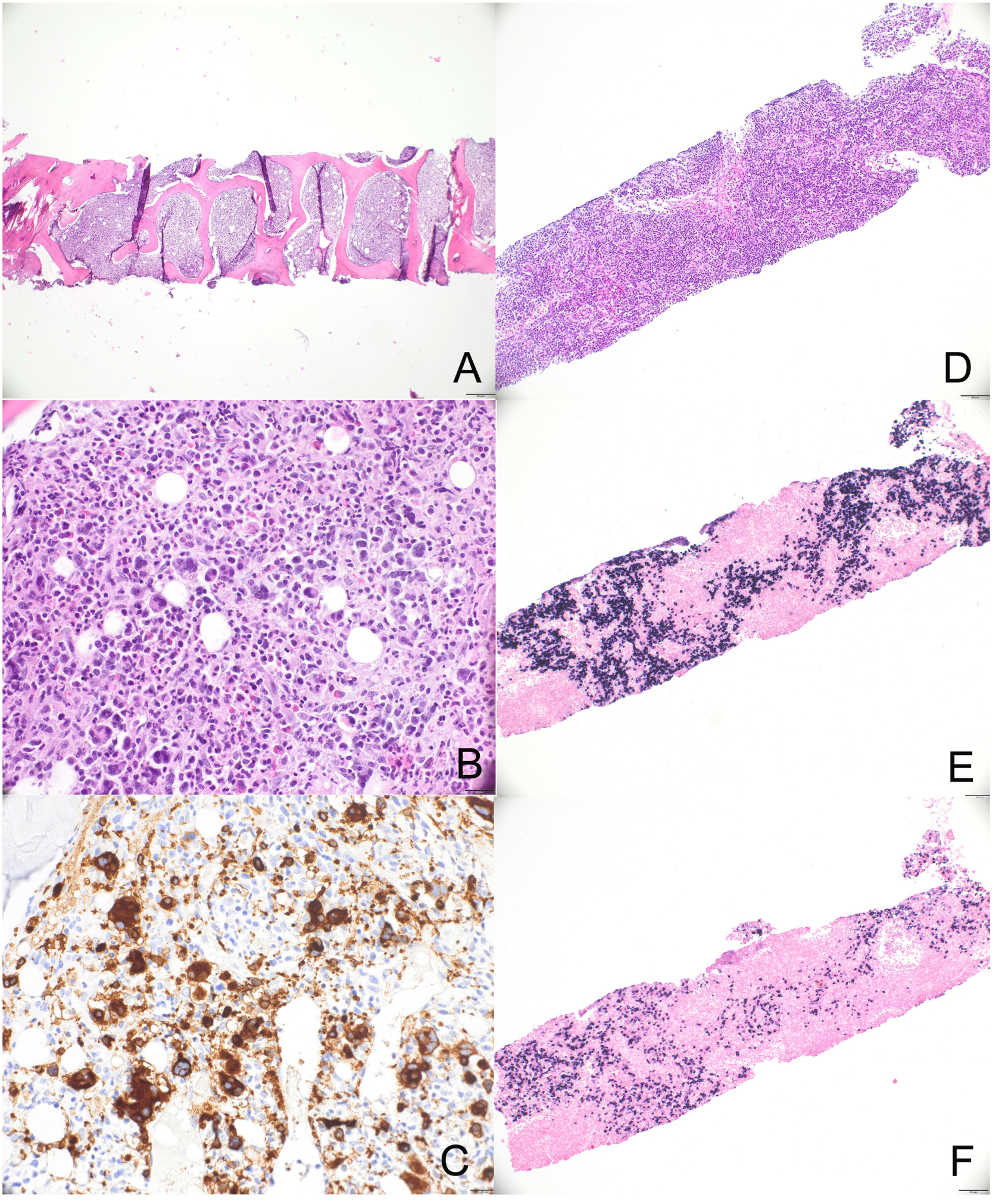
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