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ORIGINAL ARTICLE

Bone marrow findings of idiopathic Multicentric Castleman disease: A histopathologic analysis and systematic literature review

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Abstract

Idiopathic multicentric Castleman disease (iMCD) is a polyclonal lymphoproliferative disorder characterized by constitutional symptoms, generalized lymphadenopathy, cytopenias, and multi-organ dysfunction due to excessive cytokines, notably Interleukin-6. Idiopathic multicentric Castleman disease is often subclassified into iMCD-TAFRO, which is associated with thrombocytopenia (T), anasarca (A), fever/elevated C-reactive protein (F), renal dysfunction (R), and organomegaly (O), and iMCD not otherwise specified (iMCD-NOS), which is typically associated with thrombocytosis and hypergammaglobulinemia. The diagnosis of iMCD is challenging as consensus clinico-pathological diagnostic criteria were only recently established and include several non-specific lymph node histopathological features. Identification of further clinico-pathological features commonly found in iMCD could contribute to more accurate and timely diagnoses. We set out to characterize bone marrow (BM) histopathological features in iMCD, assess differences between iMCD-TAFRO and iMCD-NOS, and determine if these findings are specific to iMCD. Examination of BM specimens from 24 iMCD patients revealed a high proportion with hypercellularity, megakaryocytic atypia, reticulin fibrosis, and plasmacytosis across patients with both iMCD-NOS and iMCD-TAFRO with significantly more megakaryocytic hyperplasia ($p = 0.001$) in the iMCD-TAFRO cases. These findings were also consistent with BM findings from 185 published cases of iMCD-NOS and iMCD-TAFRO. However, these findings are relatively nonspecific as they can be seen in various other infectious, malignant, and autoimmune diseases.

KEYWORDS

bone marrow, castleman disease, iMCD, megakaryocytic hyperplasia, plasmacytosis, reticulin fibrosis

1 | INTRODUCTION

Multicentric Castleman disease (MCD) describes a heterogeneous group of polyclonal lymphoproliferative disorders characterized by intense episodic systemic inflammatory symptoms, generalized lymphadenopathy, cytopenias, and multi-organ dysfunction.[1] Clinical symptoms and disease pathogenesis are driven by excessive cytokines, often including Interleukin-6 (IL-6).[2,3] There are currently three recognized subtypes. Uncontrolled infection with human herpesvirus-8 (HHV8) causes the hypercytokinemia in

HHV8-positive MCD, and a monoclonal plasma cell population likely drives disease in polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS)-associated MCD.[4-6] However, the etiology of HHV8-negative or idiopathic MCD (Idiopathic multicentric Castleman disease (iMCD)) is unknown.

Consensus diagnostic criteria for iMCD require characteristic lymph node histopathology and multicentric lymphadenopathy (both Major Criteria), the presence of at least two of 11 Minor Criteria with at least one laboratory abnormality, and the exclusion of specific infectious, malignant, and autoimmune disorders.[1] Characteristic lymph node histopathological features include varying degrees of atrophic or hyperplastic germinal centers, follicular dendritic cell prominence, hypervascularity, and plasmacytosis. These features are often used to classify patients into the hyaline vascular/hypervascular, mixed, or plasmacytic histopathological subtypes; limited data exist to indicate clinical relevance of these subtypes.[7]

Recently, patients have been divided into clinical subtypes with prognostic implications, including patients with thrombocytopenia, anasarca, fever/elevated C-reactive protein, reticulin myelofibrosis/renal failure, and organomegaly, referred to as the TAFRO subtype of iMCD (iMCD-TAFRO).[8-11] Other patients, referred to here as iMCD not otherwise specified (iMCD-NOS) are less well characterized but often demonstrate thrombocytosis, hypergammaglobulinemia, and more mild symptoms.[12]

Despite the recently defined diagnostic criteria and subtypes, diagnosis of iMCD based on lymph node histopathology, clinical abnormalities, and laboratory testing remains challenging. The complex clinical presentation involves extensive lymphadenopathy and laboratory abnormalities often found with lymphomas, leukemias, and other blood disorders. Patients therefore frequently undergo bone marrow (BM) biopsy and histopathological review as part of their diagnostic work up. Myelofibrosis is included as a feature in multiple TAFRO definitions.[9] However, BM findings in iMCD have not been formally characterized nor described in diagnostic guidelines.

Histopathological features reported in BM from iMCD cases and related conditions can include changes in cellularity, megakaryocyte count, dysplastic changes, plasma cell count, and fibrosis.[13] In normal individuals, BM cellularity gradually decreases with age. Autoimmunity, infections, dysregulated levels of cytokines, and malignancies can lead to hypercellularity or hypocellularity.[13,14] Megakaryocytes are large, multi-lobulated platelet-generating cells that can be increased in number, abnormal in size, and contain nuclei that are more lobulated than expected in thrombocytopenic disorders,[15] myelodysplastic syndromes (MDS),[16] and myeloproliferative neoplasms (MPN).[17] Occasionally, the movement of blood cells such as erythrocytes, lymphocytes, and neutrophils without their destruction through megakaryocytes, which is referred to as emperipolesis, has been reported in myeloid neoplasms,[18] non-Hodgkin lymphoma,[19] idiopathic thrombocytopenia purpura,[20] and reactive thrombocytosis.[21] Plasma cells are antibody producing cells that reside in the BM, spleen, and lymph nodes. Increased numbers of polytypic plasma cells can be found in neoplastic, autoimmune and liver diseases, and infections. Monoclonal plasmacytosis is found in malignancies and pre-malignancies.[22,23] Reticulin fibrosis can be seen in primary myelofibrosis,[24] essential thrombocytopenia,[25] MDS,[26] and inflammatory conditions. Characterizing the frequency of these features in iMCD may provide insights into pathogenesis and possible new diagnostic features in iMCD.

Herein, we report the findings of a BM histopathological study in iMCD. We examined BM specimens from 24 iMCD patients and systematically reviewed BM findings from 185 published iMCD cases, as well as 1852 cases with related disorders, to characterize BM histopathological features in iMCD, assess differences between iMCD-TAFRO and iMCD-NOS, and understand BM features in iMCD in the context of other similar disorders to determine whether these findings are specific to iMCD.

2 | METHODS

2.1 | Tissue specimens

Tissue specimens were obtained from 24 iMCD patients enrolled in the ACCELERATE natural history registry (NCT02817997) who met clinical and laboratory criteria for iMCD and who had BM tissue banked from prior procedures.[1] BM core biopsies were performed as part of routine clinical care, with 19 of 24 BM specimens collected during disease flare occurring within 90 days of iMCD diagnosis and 5 of 24 specimens collected during subsequent periods of disease flare. Tissue specimens were requested from the patient's treating institution under the ACCELERATE protocol and processed at the University of Pennsylvania for review. For patients with multiple specimens available, one specimen was selected for review. All patients consented to the research.

2.2 | Pathology review

Hematoxylin and eosin (H&E)-stained sections of BM were reviewed by three hematopathologists for 13 of the 24 cases. Subsequently, an additional 11 cases were obtained and reviewed by one of the threehematopathologists who reviewed the first cohort. Morphologic findings and, when available, reticulin staining and immunophenotypic findings, were systematically assessed and recorded for each specimen. In all 24 cases, cellularity, plasmacytosis, myeloid/erythroid ratio, megakaryocytic hyperplasia, megakaryocytic atypia, reticulin fibrosis, and presence of lymphoid aggregates were assessed; data from clinical BM pathology reports supplemented features as needed. After observing increased megakaryocytic atypia in the initial cohort, further characterization of hypolobulation, hypochromasia, clustering, dysmegakaryopoiesis, and cytologic atypia was performed in the second cohort of 11 cases. Megakaryocytic

atypia and megakaryocytic dysplasia were measured and categorized by degree with 1%–9% considered minimal, 10%–19% mild, 20%–29% moderate, and ≥30% marked. When present, reticulin fibrosis was categorized as mild (grade 1), moderate (grade 2), and marked (grade 3).[27] As CD138 staining was not available for all patients for direct review by pathologists, reports of plasmacytosis were extracted from the ACCELERATE registry. Paired clinical and laboratory data were also obtained from the ACCELERATE registry. Based on review of these findings and on current guidelines,[1,8] patients were categorized into those with iMCD-NOS ($N = 11$ patients) and those with iMCD-TAFRO ($N = 13$ patients). Fisher's exact test was used to compare the proportions of given features between iMCD-TAFRO and iMCD-NOS, and Mann-Whitney test was used to compare sample means with $\alpha = 0.05$ for all comparisons. Analyses were performed using *R* version 4.0.4. Data are available upon reasonable request.

2.3 | Systematic literature reviews

Two systematic literature reviews were performed. The first was a review of iMCD cases with BM descriptions performed by searching PubMed for "TAFRO," "Castleman," and "Castleman's" in October 2020. Data on 185 iMCD cases were found and extracted. HHV-8 status was not specified in 12 of the iMCD-TAFRO cases and one of the iMCD-NOS cases. Features were included in the analysis when reported; many case reports did not present information on all BM features.

The second systematic literature review was conducted on BM descriptions in 17 clinico-pathologically overlapping diseases: hemophagocytic lymphohistiocytosis, adult onset Still's disease, systemic lupus erythematosus, Sjogren syndrome, IgG4-related disease, autoimmune lymphoproliferative syndrome, autoimmune myelofibrosis (AIMF), POEMS syndrome, Hodgkin lymphoma, multiple myeloma, angioimmunoblastic T cell lymphoma (AITL), Langerhan's cell histiocytosis, post-transplant lymphoproliferative disorder, MDS, MPN, HHV8-associated MCD (HHV8-associated MCD), Epstein-barr virus (EBV)-infection, and human immunodeficiency virus (HIV)-infection. The literature review was performed in December 2020 by searching PubMed for each given disease paired with the following phrases: BM, BM hypercellularity, megakaryocytic hyperplasia, megakaryocytic atypia, reticulin fibrosis, and plasmacytosis. The MeSH terms were searched in various combinations in order to increase search sensitivity. References for both literature reviews can be found in the Supplemental document.

3 | RESULTS

Of the 24 iMCD patients included in this study, 16 were males and eight were females with an average age at diagnosis of 32.3 years (range: 3–62.6 years; Table 1). iMCD-TAFRO patients tended to be younger and have hypervascular lymph node histopathologic features more frequently than iMCD-NOS. iMCD-NOS had fewer abnormal lab values except for IgG, which was more elevated. About half of BM biopsies were performed before iMCD diagnosis but all biopsies were performed during active iMCD symptoms. See Table S1 for individual patient data.

Across all 24 reviewed iMCD cases, BMs tended to be hypercellular for age (iMCD-TAFRO: 10/13, iMCD-NOS: 4/11) compared to what would be expected in healthy individuals (normocellular).[28] The proportion of patients with plasma cells >5% tended to be increased in iMCD cases (iMCD-TAFRO: 4/10, iMCD-NOS: 6/10) compared to what would be expected in healthy individuals (plasma cells <2%).[29] Median age of patients with plasma cells <5% was 27 (range: 3–70) compared to 43.5 for patients with plasma cells ≥5% (range 14–49). Given this, we examined the effect of age and clinical subtype on the presence of plasma cells ≥5%, which was not significant ($p = 0.179$). All samples were collected during active disease (within 90 days of disease flare onset).

Megakaryocytic atypia and reticulin fibrosis were frequently present across iMCD-TAFRO (8/13 and 6/9, respectively) and iMCD-NOS (5/11 and 3/6, respectively) cases; these features are not expected in normal BM. The megakaryocytic atypia and reticulin fibrosis tended to be mild/low grade. Atypia included hypolobulation (4 iMCD-TAFRO, 3 iMCD-NOS), hyperchromasia (3 iMCD-TAFRO, 2 iMCD-NOS), and clustering (2 iMCD-TAFRO, 2 iMCD-NOS; Figure 1). Bone marrow findings for reviewed cases can be found in Table 2, and representative BM images can be found in Figure 1.

When comparing between clinical subtypes, there was a difference in the cellularity (10 hypercellular, two hypocellular, one normocellular [iMCD-TAFRO] versus four hypercellular, one hypocellular, six normocellular [iMCD-NOS], $p = 0.029$) and megakaryocytic hyperplasia (9/13 [iMCD-TAFRO] versus 0/11 [iMCD-NOS]; $p = 0.001$). Emperipolesis was assessed in 6 iMCD-TAFRO patients and 6 iMCD-NOS patients; it was found in 5 of 6 iMCD-TAFRO patients and 1 of 6 iMCD-NOS patients, but this was not statistically compared due to small sample sizes. No cases in either subgroup contained lymphoid aggregates resembling iMCD lymph node histopathology. Table S2 demonstrates the distribution of BM features across the different lymph node histopathological subtypes. Megakaryocytic hyperplasia and megakaryocytic atypia were noted frequently among cases with hypervascular subtype. These results are consistent with the trends identified in iMCD-TAFRO patients, of whom 10/13 (77%) had hypervascular lymph nodes. Both patients with plasmacytic lymph nodes expectedly demonstrated plasma cells >5%, with one >10%. To validate these findings in an independent series of cases, we performed a systematic literature review of iMCD cases with BM histopathology described. We identified 132 published case reports of iMCD-TAFRO and 53 cases of iMCD-NOS (Table 3). Consistent with our histopathologic analysis, hypercellularity was commonly found in both iMCD-TAFRO (36/72 50%) and iMCD-NOS (11/27 40.7%) cases in the published literature. Megakaryocytic hyperplasia, megakaryocytic atypia, and reticulin fibrosis were each found to occur in both clinical subgroups with a

TABLE 1 Clinical features of bone marrow (BM) biopsies reviewed

	All patients N = 24	iMCD-TAFRO N = 13	iMCD-NOS N = 11
Gender, N (%)			
Female	8 (33)	4 (31)	4 (36)
Male	16 (66)	9 (69)	7 (64)
Age at diagnosis			
Mean (Standard deviation [SD])	32.3 (16)	25.3 (14)	40.5 (14)
Race, N (%)			
White	12 (50)	7 (54)	5 (46)
Black	2 (8)	1 (8)	1 (9)
Asian	4 (17)	2 (15)	2 (18)
Other	6 (25)	3 (23)	3 (27)
Histopathological subtype, N (%)			
Hypervascular	14 (58)	10 (77)	4 (36)
Mixed	7 (29)	3 (23)	4 (36)
Plasmacytic	2 (8)	0	2 (18)
Unknown	1 (5)	0	1 (9)
Constitutional symptoms, N (%)			
Yes	20 (87)	12 (92)	8 (80)
No	3 (13)	1 (8)	2 (20)
Not assessed	1	0	1
Organomegaly, N (%)			
Yes	20 (87)	13 (100)	7 (70)
No	3 (13)	0	3 (30)
Not assessed	1	0	1
Fluid accumulation, N (%)			
Yes	17 (77)	13 (100)	4 (44)
No	5 (23)	0	5 (56)
Not assessed	2	0	2
C-reactive protein, mg/L			
N assessed	21	12	9
Mean (SD)	81.1 (85)	91.7 (93)	67.0 (69)
Hemoglobin, g/dL			
N assessed	22	13	9
Mean (SD)	9.3 (2)	8.6 (2)	10.1 (3)
Platelets, k/uL			
N assessed	22	13	9
Mean (SD)	198.5 (172)	105.5 (139)	332.8 (126)
Albumin, g/dL			
N assessed	22	13	9
Mean (SD)	2.6 (1)	2.3 (1)	3.0 (1)
Creatinine, mg/dL			
N assessed	22	13	9
Mean (SD)	1.1 (1)	1.2 (1)	0.9 (0.19)

TABLE 1 (Continued)

	All patients $N = 24$	iMCD-TAFRO $N = 13$	iMCD-NOS $N = 11$
IgG, mg/dL			
N assessed	19	12	7
Mean (SD)	2300.4 (1688)	1687.2 (1140)	3351.6 (2031)

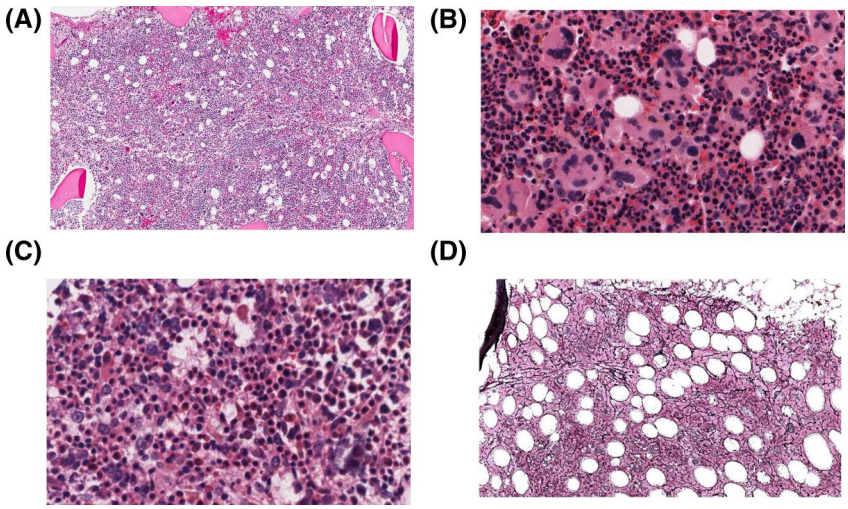

FIGURE 1 Representative images of Idiopathic multicentric Castleman disease (iMCD) bone marrow (BM) core biopsies. (A) Hypercellularity demonstrated by hematoxylin and eosin stain at 10X magnification, (B) megakaryocytic hyperplasia and atypia demonstrated at 40X, (C) plasmacytosis demonstrated at 40X, and (D) reticulin fibrosis demonstrated at 5X magnification

significantly increased frequently in iMCD-TAFRO compared with iMCD-NOS (all $p < 0.001$). Plasmacytosis was noted in a higher percentage of iMCD-NOS cases, but this was not significant ($p = 0.118$). Demonstration of our findings in the case series review and from the literature review can be found in Figure 2.

Given that these BM histopathologic findings were consistently observed in both our cohort and the published literature and the need for specific histopathology to improve diagnosis, we investigated the presence of these features in 17 clinico-pathologically overlapping diseases through secondary research of the published literature, as described in Methods (Figure 3). Of note, in all 17 clinico-pathologically overlapping diseases, at least one of the five BM features observed in iMCD has been reported. Systemic lupus erythematosus, multiple myeloma, AITL, AIMF, HHV8-associated MCD, and HIV infection were the only diseases that have been reported to demonstrate all five features though data are sparse with the smallest report including a single case and the largest including 586 patients.

4 | DISCUSSION

In this study, we report the largest and most comprehensive analysis of BM histopathology in iMCD to date. A detailed assessment of histopathological features was performed on 24 iMCD BM specimens, including 13 iMCD-TAFRO and 11 iMCD-NOS. A literature review was subsequently performed to describe these features as reported in 185 published iMCD cases. The most notable changes present in both clinical subgroups of iMCD were hypercellularity, megakaryocyte atypia, mild to moderate reticulin fibrosis, and polyclonal plasmacytosis. Megakaryocytic hyperplasia and emperipolesis were more common in iMCD-TAFRO.

Hypercellularity ranged from 60% to 90% and was noted in all three lineages but was especially prominent in megakaryocytes. The megakaryocytic hyperplasia found more commonly in the iMCD-TAFRO cases may represent a response to severe thrombocytopenia, which is likely due to immune mediated peripheral platelet destruction possibly secondary to antiplatelet antibodies. Alternatively, it is possible that the thrombocytopenia could be secondary to dysfunctional megakaryocytes, as megakaryocytic atypia was noted in most cases. Atypical forms include presence of hypolobulated, hyperchromatic forms. Clustering was commonly noted and emperipolesis was common in iMCD-TAFRO. Elevated IL-6, which is found in both iMCD-TAFRO cases with low platelets and iMCD-NOS cases with normal or elevated platelet counts, has been reported to cause increased megakaryocytes and may contribute to this in iMCD.[30-33]

Megakaryocytic atypia and dysplasia are associated with low platelet counts in other conditions,[34] which is consistent with our findings for the iMCD-TAFRO cases, but it does not explain why the iMCD-NOS patients who often have mildly or moderately elevated platelet counts also have megakaryocytic atypia. A possible explanation for the atypia in iMCD-NOS may be the hypercytokinemia observed in iMCD-NOS.

Regardless of etiology, megakaryocytic atypia may be useful in distinguishing iMCD from other overlapping disorders. Likewise, reticulin fibrosis was also present in both iMCD-NOS and

TABLE 2 Histologic features of Idiopathic multicentric Castleman disease (iMCD) bone marrow (BM) biopsies

	All iMCD *N* = 24	iMCD-TAFRO *N* = 13	iMCD-NOS *N* = 11	*p*-value	Expected results in healthy bone marrow
Cellularity					
Hypercellular, N (%)	14 (58.3)	10 (76.9)	4 (36.4)		
Hypocellular, N (%)	3 (12.5)	2 (15.4)	1 (9.1)	0.029	Normocellular[28]
Normocellular, N (%)	7 (29.2)	1 (7.7)	6 (54.5)		
Cellularity %					
Mean (SD)	72.2 (21.2)	83.5 (12.0)	57.5 (22.0)	0.005	2.4 (0.49)[40]
Confidence interval (CI)	63.7, 80.7	77.0, 90.0	44.4, 70.5		
M/E Ratio value					
Mean (SD)	7.44 (15.7)	10.7 (20.5)	3.1 (1.2)	0.249	2.4 (0.49)[40]
CI	1.15, 13.7	0.0,21.9	2.4, 3.8		
Plasma cell %					
<5, N (%)	10 (50)	6 (60)	4 (40)		
5–10, N (%)	9 (45)	4 (40)	5 (50)	0.432	<2%[29]
>10, N (%)	1 (5)	0	1 (10)		
Not documented	4	3	1		
Megakaryocytic hyperplasia					
Yes	9 (37.5)	9 (69.2)	0	0.001	Not increased[41]
No	15 (62.5)	4 (30.8)	11 (100.0)		
Megakaryocytic atypia					
Yes	13 (54.2)	8 (61.5)	5 (45.5)	1.000	Not present[29]
No	11 (45.8)	5 (38.5)	6 (54.5)		
Degree of atypia					
Minimal	7 (29.2)	2 (15.4)	5 (45.5)		
Mild	10 (41.7)	5 (38.5)	5 (45.5)	0.383	Not present[29]
Moderate	3 (12.5)	3 (23.1)	0		
None	4 (16.7)	3 (23.1)	1 (9.1)		
Hypolobulation					
Yes	7 (63.6)	4 (80)	3 (50)		
No	4 (36.4)	1 (20)	3 (50)	0.546	Not present[29]
Not documented	13	8	5		
Hyperchromasia					
Yes	5 (45.5)	3 (60)	2 (33.3)		
No	6 (54.5)	2 (20)	4 (66.7)	0.567	Not present[29]
Not documented	13	8	5		
Clustering					
Yes	4 (36.4)	2 (40)	2 (33.3)		
No	7 (63.6)	3 (60)	4 (66.7)	1.000	Not present[29]
Not documented	13	8	5		
Percent abnormal megakaryocytes					
Mean (SD)	9.7 (7.2)	11.1 (8.4)	8.1 (5.6)	0.486	Not present[29]
CI	6.8, 12.7	6.6, 15.7	4.8, 11.4		

TABLE 2 (Continued)

	All iMCD $N = 24$	iMCD-TAFRO $N = 13$	iMCD-NOS $N = 11$	p-value	Expected results in healthy bone marrow
Emperipolesis					
Yes	6 (50)	5 (83.3)	1 (16.7)		
No	6 (50)	1 (16.7)	5 (83.3)	NA	'Occasional'[29]
Not assessed	12	7	5		
Dysmegakaryopoiesis					
Yes	8 (72.7)	4 (80)	4 (66.7)		
No	3 (27.3)	1 (20)	2 (33.3)	NA	Not present[41]
Not documented	13	8	5		
Cytologic atypia					
Yes	8 (72.7)	4 (80)	4 (66.7)		
No	3 (27.3)	1 (20)	2 (33.3)	NA	Not present
Not documented	13	8	5		
Aberrant clustering					
Yes	6 (60)	3 (60)	3 (60)		
No	4 (40)	2 (40)	2 (40)	NA	Not present[29]
Not documented	14	8	6		
Megakaryocytic dysplasia					
Minimal	2 (18.2)	1 (20)	1 (16.7)		
Mild	7 (63.6)	3 (60)	4 (66.7)		
Moderate	1 (9.1)	1 (20)	0	NA	Not present[41]
None	1 (9.1)	0	1 (16.7)		
Not documented	13	8	5		
Reticulin fibrosis					
Increased	9 (60)	6 (66.7)	3 (50)		
Not increased	6 (40)	3 (33.3)	3 (50)	NA	Not present[29]
Not documented	9	4	5		
Increased reticulin, grade					
Grade 1	6 (75)	5 (83.3)	1 (50)		
Grade 2	2 (25)	1 (16.7)	1 (50)	NA	Not applicable
Not documented	1	0	1		
Lymphoid aggregates					
Yes	0	0	0	NA	Not present
No	24 (100)	13 (100)	11 (100)		

iMCD-TAFRO cases, suggesting that it may contribute to the constellation of features seen in iMCD. The underlying etiology of BM fibrosis is not well understood. However, increases in stromal fibers are commonly observed in many inflammatory, autoimmune, infectious and neoplastic processes.[35] As expected, we found fibrosis in a number of condition in our systematic literature review including MDS/MPN, AIMF, and others. Inflammatory cytokines are believed to induce fibroblasts to produce growth factors and induce fibrotic changes.[36]

Plasmacytosis was present in both iMCD-NOS and iMCD-TAFRO with a non-significantly increased frequency in the iMCD-NOS cases. This is consistent with the finding of polyclonal hypergammaglobulinemia being more common in iMCD-NOS than iMCD-TAFRO. Increased plasma cells in BM would be expected to generate

	iMCD-TAFRO (N = 132)	iMCD-NOS (N = 53)	p-value
Cellularity			
Hypercellular, N/Total (%)	36/72 (50.0%)	11/27 (40.7%)	0.519
Hypocellular, N/Total (%)	9/72 (12.5%)	5/27 (18.5%)	
Normocellular, N/Total (%)	27/72 (37.5%)	7/27 (25.9%)	
Megakaryocytic hyperplasia			
N/Total (%)	50/69 (72.5%)	3/24 (12.5%)	<0.001
Megakaryocytic atypia			
N/Total (%)	35/58 (60.3%)	1/25 (4.0%)	<0.001
Reticulin fibrosis			
N/Total (%)	82/103 (79.6%)	2/29 (6.90%)	<0.001
Plasmacytosis			
N/Total (%)	6/47 (12.8%)	12/45 (26.7%)	0.118

TABLE 3 Literature review of bone marrow (BM) findings of 185 iMCD-TAFRO and iMCD not otherwise specified (iMCD-NOS) cases

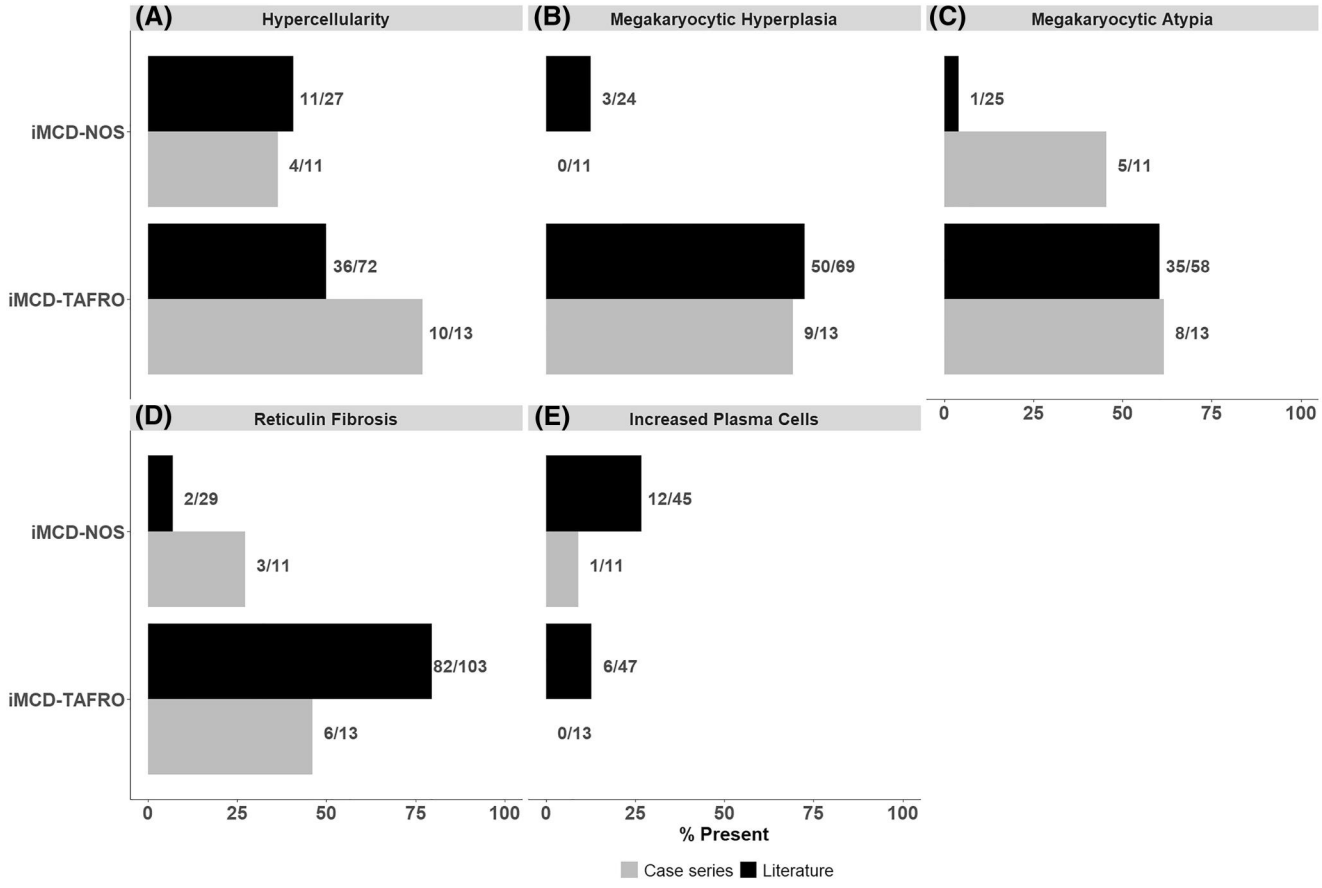

FIGURE 2 Bone marrow (BM) findings in Idiopathic multicentric Castleman disease (iMCD) as found in the case series reviewed herein and in the literature. Findings presented for (A) hypercellularity, (B) megakaryocytic hyperplasia, (C) megakaryocytic atypia, (D) reticulin fibrosis, and (E) increased plasma cells. Bars represent percent present in the literature for a given feature. Labels indicate the number of patients with a positive finding over the total number of patients identified in the case series or literature reporting that feature, respectively

increased immunoglobulins. The increased plasmacytosis and hypergammaglobulinemia in iMCD-NOS relative to iMCD-TAFRO may also reflect increased IL-6 signaling, which can promote plasma cell development.[37] Increased plasmacytosis tended to occur in older patients, which also aligns with the fact that iMCD-NOS patients tend to be older than iMCD-TAFRO. Based on this cohort, it is difficult to determine whether the increase in plasmacytosis in older individuals is independent from clinical subtype.

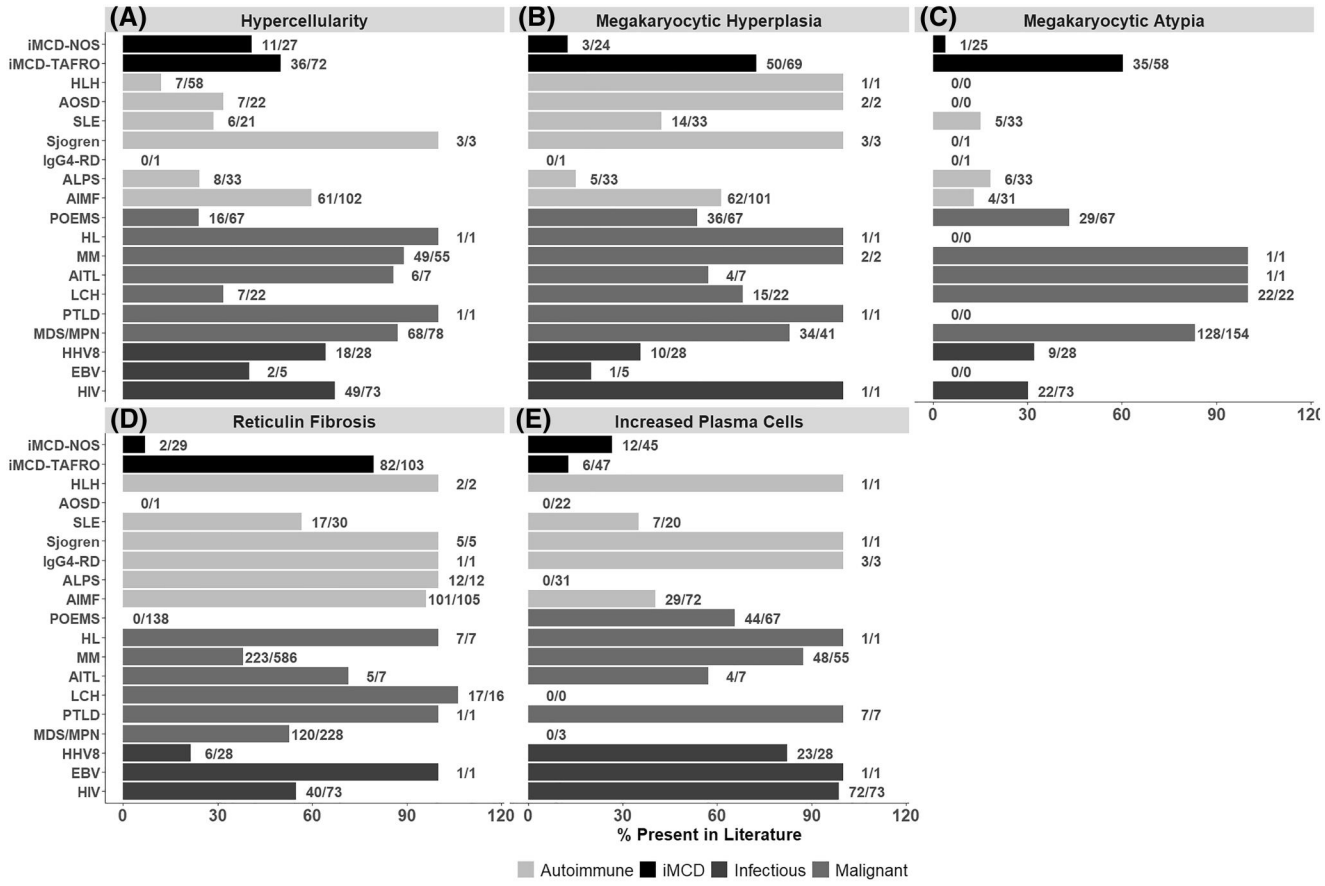

FIGURE 3 Bone marrow (BM) findings in immune disorders difficult to distinguish from Idiopathic multicentric Castleman disease (iMCD). Findings presented for (A) hypercellularity, (B) megakaryocytic hyperplasia, (C) megakaryocytic atypia, (D) reticulin fibrosis, and (E) increased plasma cells. Bars represent percent present in the literature for a given feature. Labels indicate the number of patients with a positive finding over the total number of patients identified in the literature reporting that feature

Interestingly, many of the BM features observed in our cohort were also seen in a study of BM among HHV-8-associated MCD patients, including hypercellularity, megakaryocytic hyperplasia, megakaryocytic atypia, plasmacytosis, and reticulin fibrosis.[38] While lymphoid aggregates resembling lymph node follicles were found in 5/28 HHV-8-associated MCD cases, none of the iMCD cases in our cohorts demonstrated this feature.[38] We also found that there were reports of at least one of the five BM features observed in iMCD in all 17 clinico-pathologically overlapping diseases, indicating that these features are not pathognomonic.

Although the total number of cases reviewed in-depth is small ($N = 24$), we confirmed from our systematic literature review that hypercellularity, megakaryocytic atypia, and reticulin fibrosis are common across published cases in iMCD. While none of these BM histopathological features are specific to iMCD, a constellation of these findings could be refined to support the diagnosis of iMCD within these overlapping diseases. Also importantly, these BM findings could be used to support an iMCD diagnosis when no other specific diagnoses are likely.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Elizaveta Belyaeva: Conceptualization, Investigation, Formal Analysis, Writing - Review & Editing, **Ayelet I. Rubenstein:** Investigation, Formal Analysis, Visualization, Writing - Review & Editing, **Sheila K. Pierson:** Data Curation, Supervision, Formal Analysis, Visualization,

Writing - Original Draft, Writing - Review & Editing, **Delaney Dalldorf:** Investigation, Formal Analysis, Writing - Review & Editing, **Dale Frank:** Investigation, Formal Analysis, Writing - Review & Editing, Megan S. Lim: Investigation, Formal Analysis, Writing- Review & Editing, **David C. Fajgenbaum:** Funding Acquisition, Project Administration, Writing - Original Draft, Writing - Review & Editing.

DATA AVAILABILITY STATEMENT

The original data related to the bone marrow histopathological changes are deposited at https://doi.org/10.5281/zenodo.5935274.

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REFERENCES

1. Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. *Blood*. 2017;129(12):1646-1657. https://doi.org/10.1182/blood-2016-10-746933
2. Yoshizaki K, Matsuda T, Nishimoto N, et al. Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. *Blood*. 1989;74(4):1360-1367.
3. Beck JT, Hsu SM, et al. Brief report: alleviation of systemic manifestations of Castleman's disease by monoclonal anti-interleukin-6 antibody. *N Engl J Med*. 1994;330(9):602-605. https://doi.org/10.1056/NEJM199403033300904
4. Fajgenbaum DC. Novel insights and therapeutic approaches in idiopathic multicentric Castleman disease. *Blood*. 2018;132(22):2323-2330. https://doi.org/10.1182/blood-2018-05-848671
5. Oksenhendler E, Carcelain G, Aoki Y, et al. High levels of human herpesvirus 8 viral load, human interleukin-6, interleukin-10, and C reactive protein correlate with exacerbation of multicentric castleman disease in HIV-infected patients. *Blood*. 2000;96(6):2069-2073.
6. Dispenzieri A, Armitage JO, Loe MJ, et al. The clinical spectrum of Castleman's disease. *Am J Hematol*. 2012;87(11):997-1002. https://doi.org/10.1002/ajh.23291
7. Fajgenbaum DC, Wu D, Goodman A, et al. Insufficient evidence exists to use histopathologic subtype to guide treatment of idiopathic multicentric Castleman disease. *Am J Hematol*. 2020;95(12):1553-1561. https://doi.org/10.1002/ajh.25992
8. Masaki Y, Kawabata H, Takai K, et al. Proposed diagnostic criteria, disease severity classification and treatment strategy for TAFRO syndrome, 2015 version. *Int J Hematol*. 2016;103(6):686-692. https://doi.org/10.1007/s12185-016-1979-1
9. Takai K, Nikkuni K, Shibuya H, Hashidate H. [Thrombocytopenia with mild bone marrow fibrosis accompanied by fever, pleural effusion, ascites and hepatosplenomegaly]. *Rinsho Ketsueki*. 2010;51(5):320-325.
10. Iwaki N, Sato Y, Takata K, et al. Atypical hyaline vascular-type castleman's disease with thrombocytopenia, anasarca, fever, and systemic lymphadenopathy. *J Clin Exp Hematop*. 2013;53(1):87-93. https://doi.org/10.3960/jslrt.53.87
11. Iwaki N, Fajgenbaum DC, Nabel CS, et al. Clinicopathologic analysis of TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative multicentric Castleman disease. *Am J Hematol*. 2016;91(2):220-226. https://doi.org/10.1002/ajh.24242
12. Kojima M, Nakamura N, Tsukamoto N, et al. Clinical implications of idiopathic multicentric castleman disease among Japanese: a report of 28 cases. *Int J Surg Pathol*. 2008;16(4):391-398. https://doi.org/10.1177/1066896908315812
13. Frisch B, Bartl R. *Atlas of Bone Marrow Pathology*. Kluwer Academic Publishers; 1990.
14. Tuljapurkar SR, McGuire TR, Brusnahan SK, et al. Changes in human bone marrow fat content associated with changes in hematopoietic stem cell numbers and cytokine levels with aging. *J Anat*. 2011;219(5):574-581. https://doi.org/10.1111/j.1469-7580.2011.01423.x
15. Travlos GS. Histopathology of bone marrow. *Toxicol Pathol*. 2006;34(5):566-598. https://doi.org/10.1080/01926230600964706
16. Bhasin TS, Sharma S, Manjari M, et al. Changes in megakaryocytes in cases of thrombocytopenia: bone marrow aspiration and biopsy analysis. *J Clin Diagn Res*. 2013;7(3):473-479. https://doi.org/10.7860/JCDR/2013/5085.2801
17. Malherbe JA, Fuller KA, Arshad A, et al. Megakaryocytic hyperplasia in myeloproliferative neoplasms is driven by disordered proliferative, apoptotic and epigenetic mechanisms. *J Clin Pathol*. 2016;69(2):155-163. https://doi.org/10.1136/jclinpath-2015-203177
18. Cashell AW, Buss DH. The frequency and significance of megakaryocytic emperipolesis in myeloproliferative and reactive states. *Ann Hematol*. 1992;64(6):273-276. https://doi.org/10.1007/BF01695470
19. Dzieciol J, Lemancewicz D, Kloczko J, Boguslowicz W, Lebelt A. Megakaryocytes emperipolesis in bone marrow of the patients with non-Hodgkin's lymphoma. *Folia Histochem Cytobiol*. 2001;39(Suppl 2):142-143.
20. Muhury M, Mathai AM, Rai S, Naik R, Pai MR, Sinha R. Megakaryocytic alterations in thrombocytopenia: a bone marrow aspiration study. *Indian J Pathol Microbiol*. 2009;52(4):490-494. https://doi.org/10.4103/0377-4929.56132
21. Sahebekhitiari HA, Tavassoli M. Marrow cell uptake by megakaryocytes in routine bone marrow smears during blood loss. *Scand J Haematol*. 1976;16(1):13-17. https://doi.org/10.1111/j.1600-0609.1976.tb01110.x
22. Foucar K, Chabot-Richards D, Czuchlewski D, et al. *Plasmacytosis of Bone Marrow. Diagnostic Pathology: Blood and Bone Marrow*. 2 ed. Elsevier; 2018:218-225.
23. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538-48. https://doi.org/10.1016/S1470-2045(14)70442-5
24. Kvasnicka HM, Thiele J. Prodromal myeloproliferative neoplasms: the 2008 WHO classification. *Am J Hematol*. 2010;85(1):62-NA. https://doi.org/10.1002/ajh.21543
25. Tefferi A, Thiele J, Orazi A, et al. Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: recommendations from an ad hoc international expert panel. *Blood*. 2007;110(4):1092-1097. https://doi.org/10.1182/blood-2007-04-083501
26. Lambertenghi-Deliliers G, Orazi A, Luksch R, Annaloro C, Soligo D. Myelodysplastic syndrome with increased marrow fibrosis: a distinct clinico-pathological entity. *Br J Haematol*. 1991;78(2):161-166. https://doi.org/10.1111/j.1365-2141.1991.tb04411.x
27. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and

acute leukemia. *Blood*. May 19 2016;127(20):2391-2405. https://doi.org/10.1182/blood-2016-03-643544
28. Blebea JS, Houseni M, Torigian DA, et al. Structural and functional imaging of normal bone marrow and evaluation of its age-related changes. *Semin Nucl Med*. 2007;37(3):185-194. https://doi.org/10.1053/j.semnuclmed.2007.01.002
29. Brown DC, Gatter KC. The bone marrow trephine biopsy: a review of normal histology. *Histopathology*. 1993;22(5):411-422. https://doi.org/10.1111/j.1365-2559.1993.tb00154.x
30. Stahl CP, Zucker-Franklin D, Evatt BL, Winton EF. Effects of human interleukin-6 on megakaryocyte development and thrombocytopoiesis in primates. *Blood*. 1991;78(6):1467-1475.
31. Ishibashi T, Kimura H, Uchida T, Kariyone S, Friese P, Burstein SA. Human interleukin 6 is a direct promoter of maturation of megakaryocytes in vitro. *Proc Natl Acad Sci U S A*. 1989;86(15):5953-5957. https://doi.org/10.1073/pnas.86.15.5953
32. Lotem J, Shabo Y, Sachs L. Regulation of megakaryocyte development by interleukin-6. *Blood*. 1989;74(5):1545-1551.
33. Warren MK, Conroy LB, Rose JS. The role of interleukin 6 and interleukin 1 in megakaryocyte development. *Exp Hematol*. 1989;17(11):1095-1099.
34. Feng G, Gale RP, Cui W, et al. A systematic classification of megakaryocytic dysplasia and its impact on prognosis for patients with myelodysplastic syndromes. *Exp Hematol Oncol*. 2015;5:12. https://doi.org/10.1186/s40164-016-0041-6
35. Kuter DJ, Bain B, Mufti G, Bagg A, Hasserjian RP. Bone marrow fibrosis: pathophysiology and clinical significance of increased bone marrow stromal fibres. *Br J Haematol*. 2007;139(3):351-362. https://doi.org/10.1111/j.1365-2141.2007.06807.x
36. Uskudar Cansu D, Uskudar Teke H, Isiksoy S, Korkmaz C. Bone marrow as a target organ of systemic lupus erythematosus: analysis of cases with myelofibrosis. *Int J Rheum Dis*. 2018;21(5):1049-1059. https://doi.org/10.1111/1756-185X.13308
37. Jourdan M, Cren M, Robert N, et al. IL-6 supports the generation of human long-lived plasma cells in combination with either APRIL or stromal cell-soluble factors. *Leukemia*. 2014;28(8):1647-1656. https://doi.org/10.1038/leu.2014.61
38. Ibrahim HA, Balachandran K, Bower M, Naresh KN. Bone marrow manifestations in multicentric Castleman disease. *Br J Haematol*. 2016;172(6):923-929. https://doi.org/10.1111/bjh.13919
39. Weng CH, Lu KY, Hu CC, Huang WH, Wang IK, Yen TH. Bone marrow pathology predicts mortality in chronic hemodialysis patients. *BioMed Res Int*. 2015;2015:1-7:160382. https://doi.org/10.1155/2015/160382
40. Bain BJ. The bone marrow aspirate of healthy subjects. *Br J Haematol*. 1996;94(1):206-209. https://doi.org/10.1046/j.1365-2141.1996.d01-1786.x
41. Deutsch VR, Tomer A. Megakaryocyte development and platelet production. *Br J Haematol*. 2006;134(5):453-466. https://doi.org/10.1111/j.1365-2141.2006.06215.x

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