Crystal-Storing Histiocytosis in Bone Marrow

A Clinicopathologic Study of Eight Cases and Review of the Literature

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ABSTRACT

Objectives: *We report the clinicopathologic characteristics of eight cases of crystal-storing histiocytosis (CSH) with bone marrow (BM) involvement (BM-CSH) and review CSH cases published in the English literature.*

Methods: *We queried our pathology database for BM cases with CSH mentioned in the final diagnosis/comments from June 2011 to August 2016.*

Results: *Eight cases of BM-CSH were identified. The underlying diagnoses consisted predominantly of plasma cell disorders (88%) associated with monotypic κ light chain. In BM aspirates, crystals within histiocytes exhibited a morphologic spectrum including brightly eosinophilic, needle-like, or globule-like. In BM core biopsies, the histiocytes were often in aggregates with intracellular needle-like and/or globular, refractile inclusions.*

Conclusions: *BM-CSH is a rare phenomenon and exhibits a heterogeneous crystalline and histiocytic appearance warranting accurate recognition to avoid misinterpretation of a granulomatous condition or storage disorder. In addition, prompt assessment for an underlying B-cell lymphoma or clonal plasmacytic neoplasm is indicated.*

Crystal-storing histiocytosis (CSH) is a rare disorder characterized by the accumulation of nonneoplastic histiocytes containing intracytoplasmic refractile eosinophilic crystals, representing most often a lysosomal accumulation of crystallized immunoglobulin (Ig). In the vast majority of CSH cases (90%), there is an associated underlying lymphoproliferative or plasma cell disorder, particularly plasma cell myeloma (PCM), marginal zone lymphoma, lymphoplasmacytic lymphoma, and monoclonal gammopathy of undetermined significance.[1] In the remaining 10% of cases, CSH is associated with other conditions, including Fanconi syndrome, autoimmune disorders (eg, rheumatoid arthritis, eosinophilic colitis, and systemic mastocytosis), reactive inflammatory conditions, metabolic disorders, and drugs (eg, clofazimine).[1-3] The intracytoplasmic crystals are composed of Ig light and/or heavy chain fragments enriched in Ig variable regions, as recently demonstrated by mass spectrometry.[4] The vast majority of the neoplasms are κ light chain restricted without any specific heavy chain association.[1] Some variants of intracytoplasmic crystals have also been reported, including clofazimine crystals in clofazimine-induced CSH among lepromatous leprosy patients,[5-8] Charcot-Leyden crystals,[9,10] and amyloidal deposition.[11]

CSH may involve a wide variety of tissue sites, including bone marrow (BM), lymph nodes, liver, spleen, lungs, gastrointestinal tract, kidney, central nerve system, and skin. It may present as either localized (a single deposit involving only one organ or site) or generalized (multiple deposits involving more than one organ or site) forms.

While BM involvement is common in generalized CSH, isolated BM involvement does also rarely occur (~11% of cases).[1] The presence of crystal-laden histiocytes in BM specimens involved by CSH (BM-CSH) often poses a diagnostic dilemma, as they may mimic other types of histiocytic proliferations (eg, Gaucher cells and granulomatous inflammation) and neoplastic conditions (eg, rhabdomyoma and renal cell carcinoma).

Given the rarity of a diagnosis of BM-CSH, variable clinical presentations, potential for histologic misinterpretation, and relative paucity of published literature on this topic, we sought to describe the clinicopathologic features of BM-CSH cases in order to raise recognition of the diverse morphologic appearances and to promote early diagnosis for optimal patient management. In addition, we compared our findings with and reviewed the published literature on CSH that is not just restricted to BM involvement.

Materials and Methods

Case Selection and Data Retrieval

The study was approved by our institutional review board. BM cases diagnosed as CSH were retrieved from the files of Mayo Clinic Rochester Department of Laboratory Medicine and Pathology during the period from June 2011 to August 2016. One additional case was seen in consultation.

Clinical and Laboratory Data

Key clinical and laboratory data abstracted from the medical record included patient age, gender, clinical presentation, history of prior neoplasm, serum protein studies, organ(s) involved by CSH, cytogenetic and fluorescence in situ hybridization results, and clinical course including follow-up duration and survival time.

Bone Marrow Specimens

Bone marrow aspirate smears were stained with a Wright-Giemsa preparation. Bone marrow core biopsies were fixed in B5 fixative, rinsed with 10% neutral buffered formalin, and subjected to limited decalcification in RDO Gold Working Solution (Apex Engineering, Aurora, IL) prior to routine processing.

Morphologic Review

Diagnoses of the underlying neoplastic process were established according to the 2016 revision of World Health Organization classification criteria using a combination of morphologic, immunophenotypic, and/or molecular findings.[12] All peripheral blood smears, BM aspirates, and trephine biopsies were reviewed by two experienced hematopathologists (K.K.R. and A.C.). Cytologic appearances/characteristics of the cytoplasmic inclusions in histiocytes on both the aspirate smears and core biopsies were recorded.

Immunohistochemistry and In Situ Hybridization Studies

Immunohistochemical analysis was performed on 3 to 4 μm thick, formalin-fixed, paraffin-embedded sections in certain cases to assess plasma cell quantity and clonality (cases 1-5) and to elucidate the crystalline-containing histiocytes (cases 1, 2, 4-6). Primary antibodies included CD138 (MI15, Dako, Carpinteria, CA), κ (Dako), and λ (Dako) for plasma cells. Antibodies to highlight the histiocytes included CD68 (PG-M1, Leica Biosystems, Wetzlar, Germany) and/or CD163 (10D6, Leica Biosystems), In situ hybridization for κ and λ (Ventana Medical Systems, Tucson, AZ) was done on cases 1 to 4 and 6 to assess κ and λ clonality in the plasmacytic infiltrate.

Literature Search

A PubMed search of the English literature was performed using keyword "crystal-storing histiocytosis" in either title or abstract, and relevant publications were identified from 1987 to 2017.

Results

Clinical Features

Approximately 27,200 bone marrows were performed during the time frame from June 2011 and August 2016. Of the 27,200, approximately 10,880 were performed to evaluate for plasma cell dyscrasia, based on clinical, laboratory and/or radiologic findings. Of these 10,880 plasma cell bone marrow cases, approximately 2,176 were initial diagnostic evaluations. Seven cases meeting the search criteria for CSH were identified (0.2%). One additional case was seen in consultation. The patients included 7 men and 1 woman with an average age at diagnosis of 62 years (range, 40-73 years).

In six of the eight cases, the CSH was diagnosed concurrently with the underlying plasmacytic disorder (cases 2, 4-8). Case 1 was first seen at our institution 5 years after the original reported diagnosis (original diagnostic material not available to us for review), so it

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Table 1
Clinical Characteristics of Eight Cases of BM-CSH

Case No.	Age (y)/ Sex	Symptoms Prompting Workup	Prior Neoplasms	Underlying Diagnosis	Acute Renal Failure	Serum Paraprotein Level (g/dL)	Monoclonal Immunoglobulin Type	Site(s) Involved by CSH	CSH Diagnosis Prior, Concurrent, or Subsequent to BM Clonal Disorder Diagnosis	Clinical Course:
1	63/M	Persistent shoulder pain	No	Low-grade B-cell lymphoma	No	0.9	IgM κ	BM	Unknown[a]	Alive, 17 mo; persistent coexistent CSH and lymphoma; S/P chemotherapy
2	40/M	Severe headache and hypertension	No	Systemic amyloidosis with myeloma	No	NA	No apparent monoclonal protein	BM	Concurrent	Alive, 17 mo; persistent coexistent CSH and amyloidosis; S/P chemotherapy and PBSCT
3	71/M	Elevated total protein	No	PCM	Yes	2.6	IgG κ	BM, eye/orbit	Subsequent (37 months after myeloma diagnosis)	Died, 1 mo after diagnosis of CSH and relapsed myeloma
4	65/F	Thrombocytopenia, splenomegaly, and osteolytic lesions	No	PCM	No	3.1	IgA κ	BM	Concurrent	Alive, 88 mo; persistent coexistent CSH and myeloma (10%); S/P chemotherapy and PBSCT
5	55/M	Progressing fatigue	No	MGUS	No	0.7	IgG κ	BM, skin, liver[b]	Concurrent	Alive, 10 mo; persistent coexistent CSH and MGUS; S/P excision of skin lesions
6	70/M	Nausea, vomiting, and abdominal pain	No	PCM	No	1.2	IgG κ	BM, omentum	Concurrent	Alive, 41 mo; persistent coexistent CSH and residual myeloma (5%); S/P chemotherapy and PBSCT
7	73/M	Unknown	Unknown	MGUS	Unknown	Unknown	IgG κ	BM	Concurrent	Unknown
8	56/M	Renal failure and anemia	No	PCM	Yes	1.1	IgG κ	BM	Concurrent	Alive, 3 mo; limited follow-up due to recent diagnosis and care at different institution

BM, bone marrow; CSH, crystal-storing histiocytosis; Ig, immunoglobulin; MGUS, monoclonal gammopathy of uncertain significance; PBSCT, peripheral blood stem cell transplant; PCM, plasma cell myeloma; S/P, status post.
[a] Original diagnostic material 5 years prior was not available for our review.
[b] Foreign body granuloma-associated CSH instead of an Ig-related CSH.

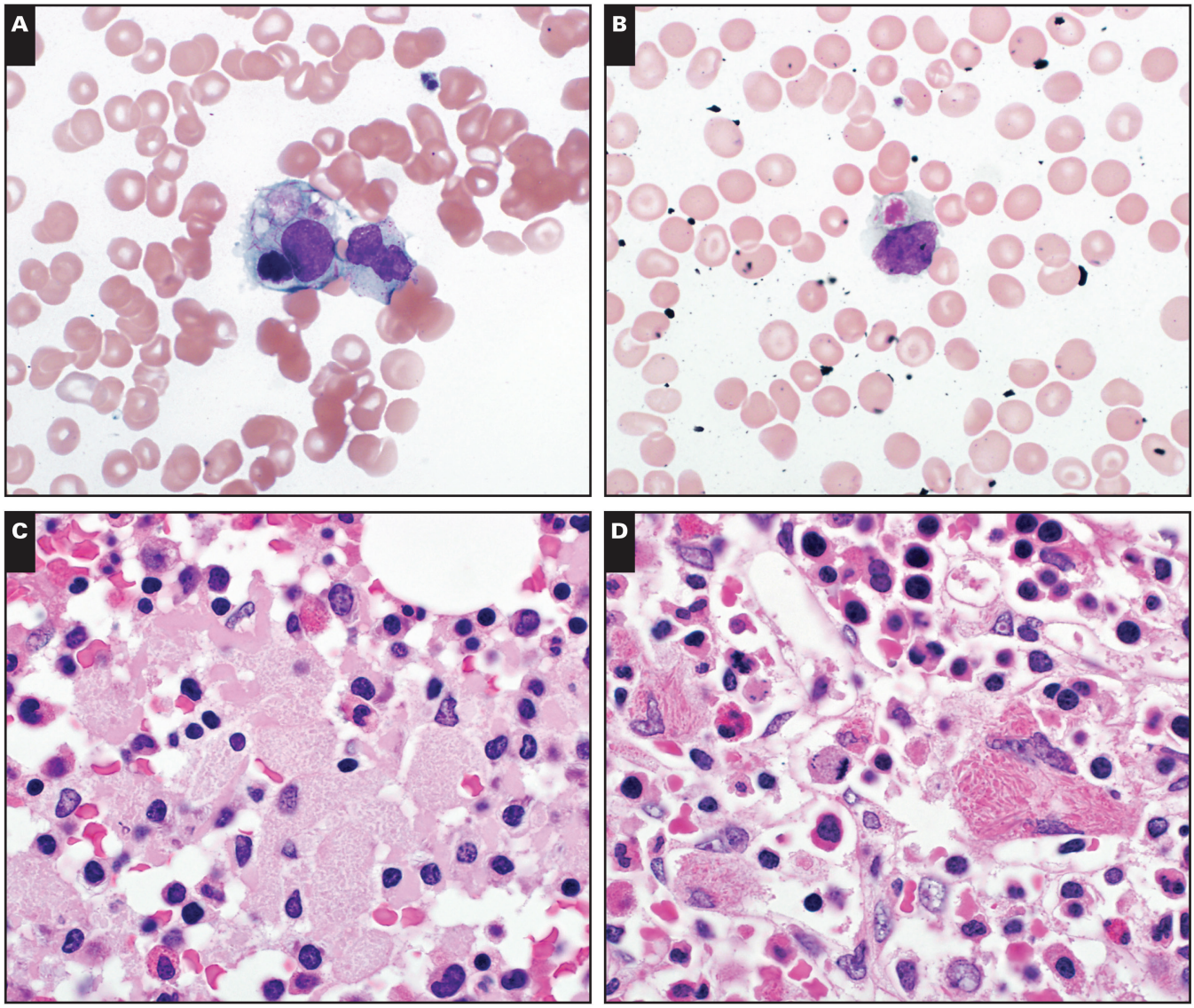

Image 1 Crystal-storing histiocytosis associated with low-grade B-cell lymphoma. The histiocytes contained slender needle-like (**A**, Wright-Giemsa, x1,000) or globular (**B**, Wright-Giemsa, x1,000) crystals. In the biopsy the histiocyte cytoplasm was lightly eosinophilic (**C**, H&E, x1,000) with occasional intracytoplasmic globular crystals (**D**, H&E, x1,000).

is not clear if CSH was present from the onset of disease or developed later in the disease course. Case 3 carried a diagnosis of PCM for 3 years prior to the development of CSH in association with his myeloma. The underlying diagnoses in the 8 BM-CSH cases consisted predominantly of plasma cell disorders including monoclonal gammopathy of undetermined significance (two cases), PCM (four cases), low-grade B-cell lymphoma (one case), and primary systemic amyloidosis associated with PCM (one case). All seven patients with available history had no prior other neoplasms.

All four PCM cases presented with typical myeloma symptoms including osteolytic lesions, acute renal failure, anemia, or elevated serum proteins (cases 3, 4, 6, and 8) Table 1. Two cases of renal failure were noted at presentation (cases 3 and 8). Two cases had history of splenomegaly but without any evidence of biopsy-proven CSH (cases 1 and 4). Case 1 had splenomegaly attributable to his lymphoma. Splenectomy, in addition to chemotherapy, had been part of his clinical treatment. Case 4 carried a prior diagnosis of immune thrombocytopenia and splenectomy had been part of the treatment regimen. Case 1 showed a very small κ light chain restricted B-cell population by splenic flow cytometry. Five cases (cases 1, 2, 4, 7, and 8) had localized BM involvement, while the remaining three had generalized involvement including BM, eye/orbit, skin, liver, and omentum. Case 2 was shown to have amyloid AL (κ)-type by mass spectrometry. All cases were

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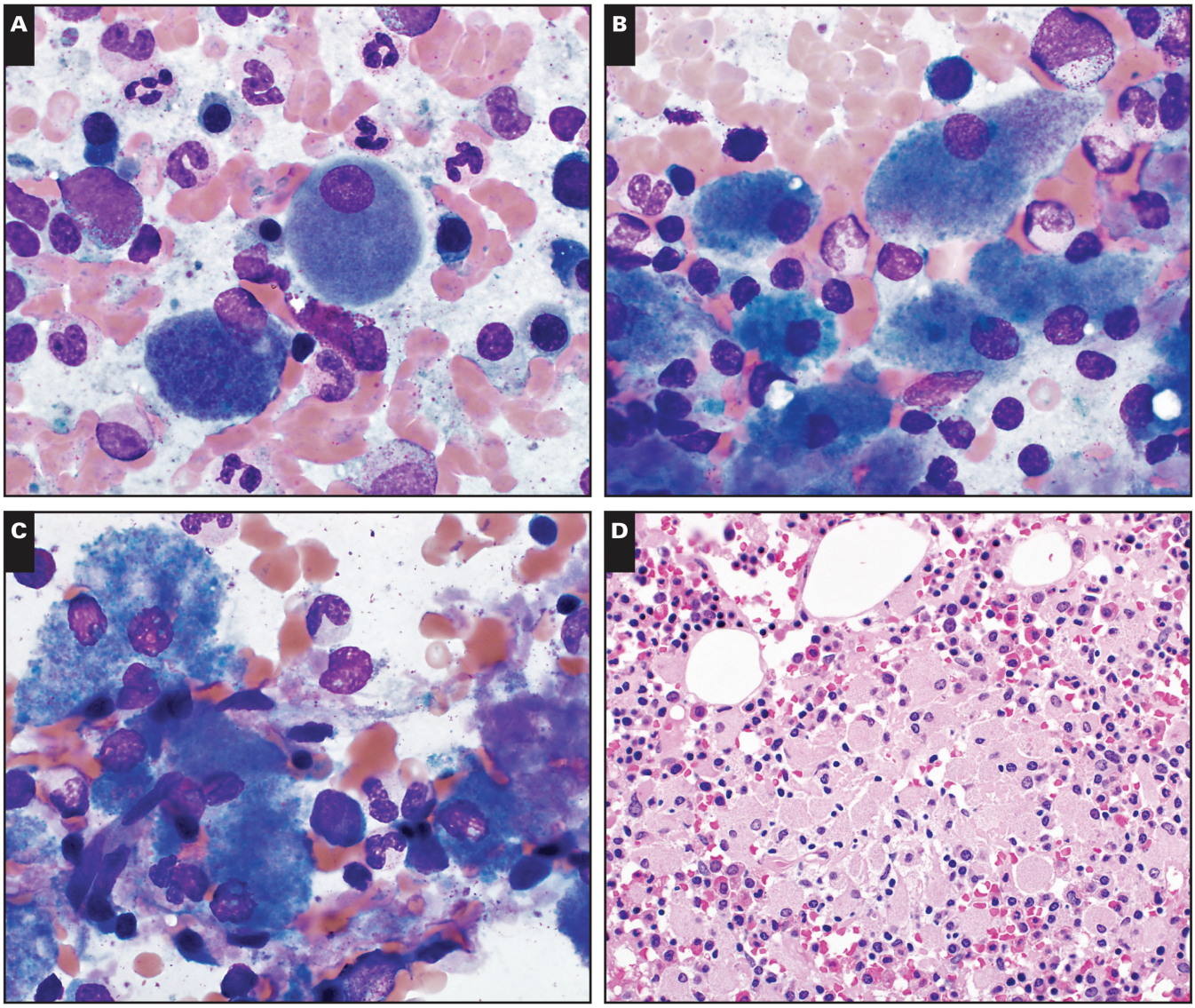

Image 2 Crystal-storing histiocytosis associated with amyloidosis and plasma cell myeloma. The histiocytes had gray-blue, finely granular cytoplasm and occasionally mimicked dysplastic small monolobated megakaryocytes (**A**, Wright-Giemsa, x1,000), or resembled sea blue histiocytes (**B**, Wright-Giemsa, x1,000). Amyloid material was seen both within the cytoplasm of the histiocytes and extracellularly (**C**, Wright-Giemsa, x1,000). In the biopsy the histiocytic infiltrate imparted a granulomatous appearance (**D**, H&E, x600).

associated with monoclonal κ light chain without association of any specific heavy chain.

Six of the seven patients were alive during the follow-up. All five cases with available follow-up biopsies showed persistent CSH after either chemotherapy or bone marrow transplantation. The patient of case 3 was followed for approximately 3 years since his diagnosis of PCM and died 1 month after CSH was identified by BM biopsy. This patient also carried a diagnosis of monoclonal gammopathy crystalline keratopathy since his initial diagnosis of PCM.

Pathologic Features

In BM aspirate smears, the crystals/crystalline inclusions within histiocytes showed a spectrum of appearances including brightly eosinophilic, needle-like, or globule-like forms **Image 1**, **Image 2**, **Image 3**, **Image 4**, **Image 5**, and **Image 6**. The cytoplasm of histiocytes could be lightly azurophilic, gray-blue, sea-blue, finely granular, lightly globular, or Gaucher-like (Image 6) **Table 2**. The histiocytes in case 2 mimicked dysplastic small monolobated megakaryocytes (Image 2A). Some of these histiocytes had sea blue cytoplasm with occasional globules while some others had

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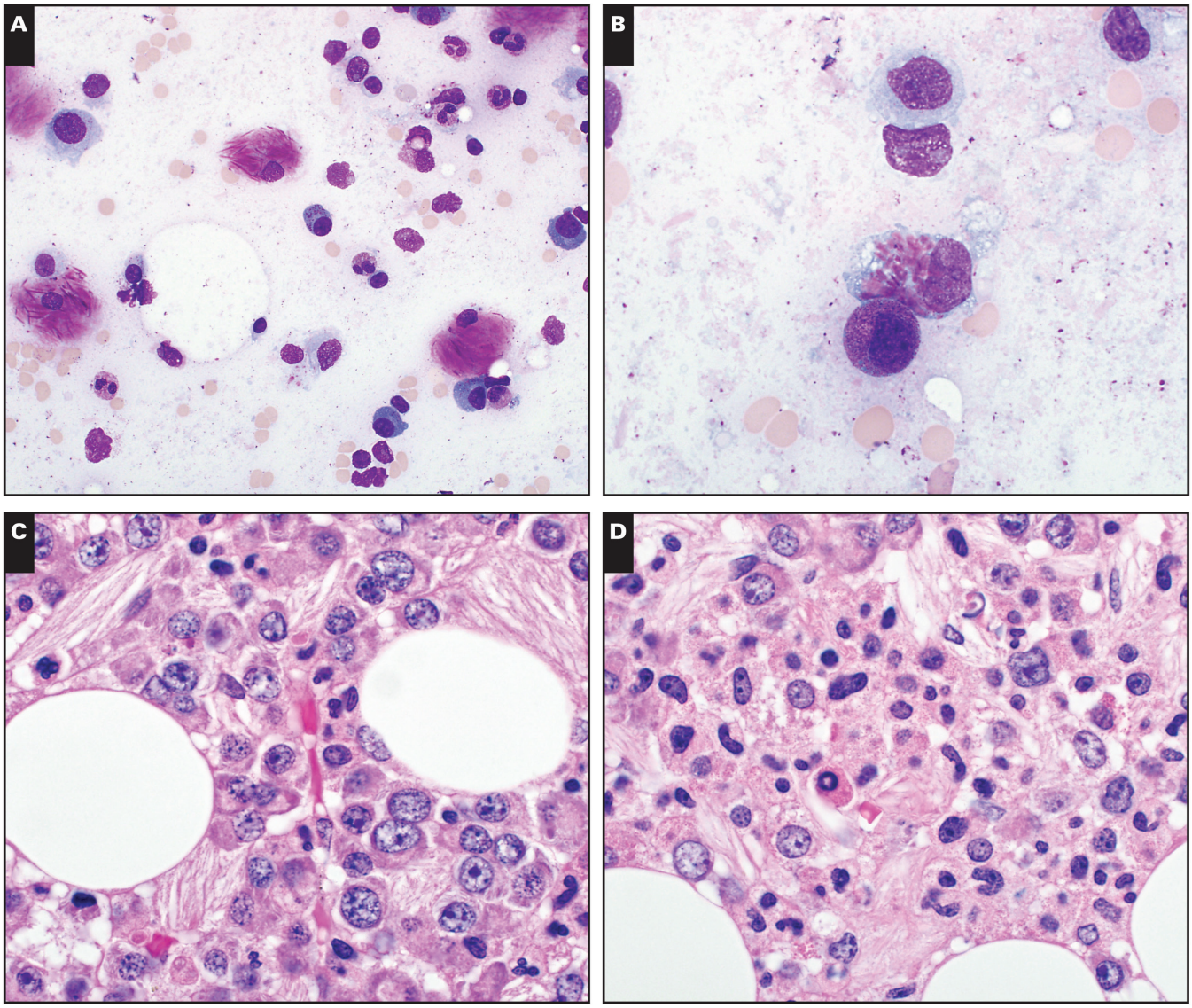

Image 3 Crystal-storing histiocytosis associated with plasma cell myeloma. The crystals were brightly eosinophilic and long and needle-like (**A**, Wright-Giemsa, x600) or globular (**B**, Wright-Giemsa, x1,000). In the biopsy the histiocytes were Gaucher-like with striated cytoplasm (**C**, H&E, x1,000) and rare globules (**D**; H&E, x1,000).

light purple cytoplasm with amyloid inclusions (Image 2C). In contrast, the histiocytes in case 3 showed brightly eosinophilic cytoplasm with numerous Auer rod-like inclusions resembling the cells seen in acute promyelocytic leukemia (APL), while some adjacent plasma cells contained large granular lymphocytic-like granules (Image 3A).

In the BM core biopsies, the histiocytes were often in aggregates, but occasionally singly distributed, with a Gaucher-like appearance on H&E with striated light pink cytoplasm and/or visible intracellular needle-like and globular, refractile inclusions (Images 3C and 3D; Table 2). Some histiocytic infiltrates imparted a granulomatous appearance (Image 2D). Case 4 showed strikingly pink histiocytes with hexagonal like crystals in biopsy (Image 4D). In this case, the plasma cells had globule-like crystals, numerous small chunky granules, or APL-like cell appearance (Images 4A-4C). The percentages of histiocytes ranged from less than 10 to well over 30 (Table 2). Case 6 demonstrated Pseudo-Gaucher histiocytes on the aspirate smear (Image 6B) while epithelioid like infiltrates were seen on the core biopsy (Images 6C and 6D).

Immunophenotypic Features

Plasma cell clonality was proven in all cases by either immunohistochemistry (cases 1-5), in situ hybridization (cases 1-4, 6) and/or flow cytometry (cases 1, 2, 3, 7, and 8) using κ and λ. In case 1, the clonal lymphoplasmacytic infiltrate was elucidated by flow cytometric immunophenotyping.

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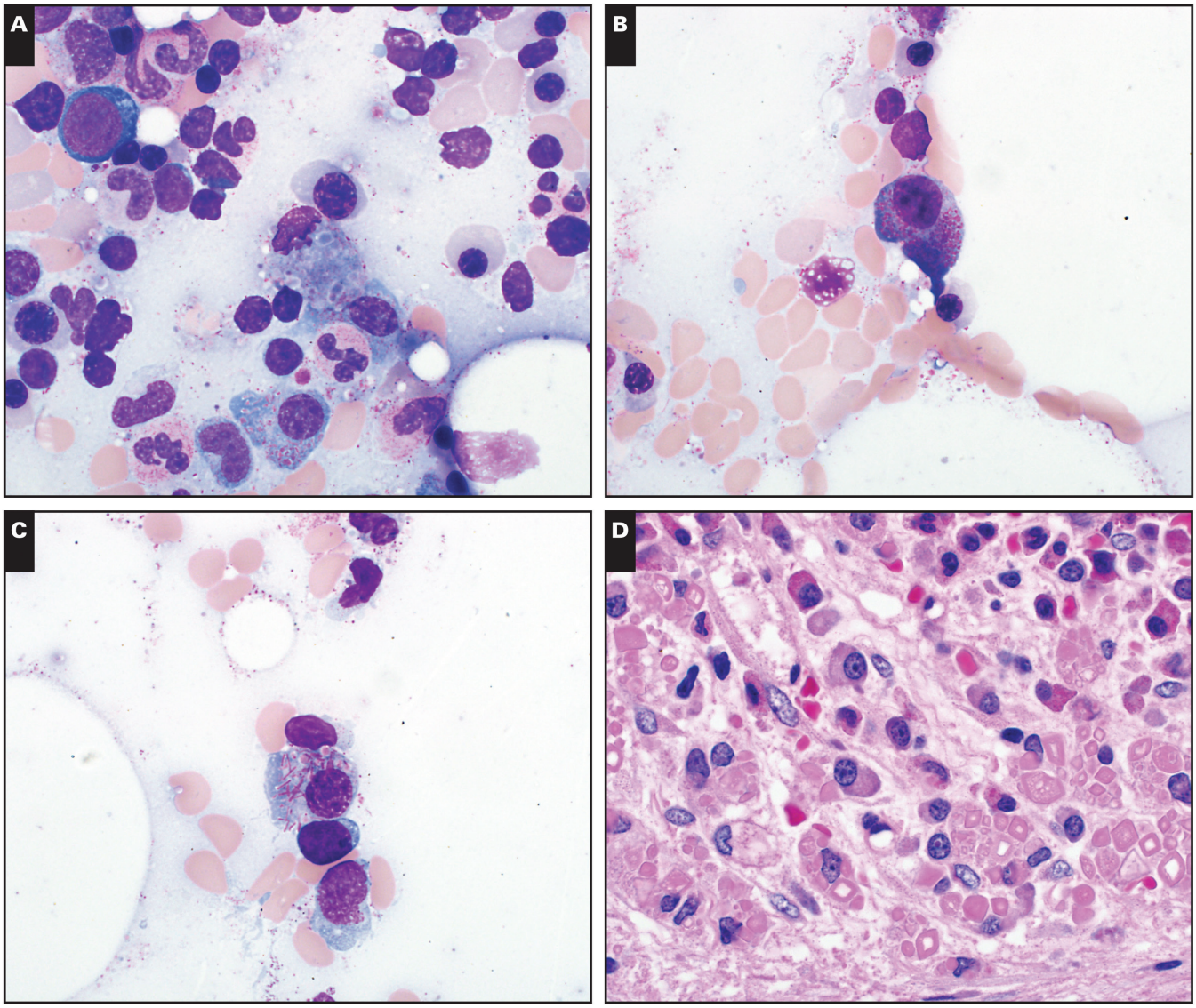

Image 4 Crystal-storing histiocytosis associated with plasma cell myeloma. The histiocytes had lightly globular cytoplasm (**A**, Wright-Giemsa, x1,000). Plasma cells had globular-like crystals (**A**), numerous small chunky granules (**B**, Wright-Giemsa, x1,000), or faggot cell appearance (**C**, Wright-Giemsa, x1,000). The biopsy showed strikingly pink histiocytes with hexagonal like crystals (**D**, H&E, x1,000).

None of the cases that had immunohistochemistry and in situ hybridization concurrently performed had a perceptible difference in the ability of the staining to detect and demonstrate plasma cell clonality **Image 7**.

Literature Review

One hundred twenty-three cases of CSH were identified through a PubMed search of the literature from 1987 to 2017. Including our eight cases, there is a total of 131. One hundred of 131 cases (76%) are associated with an underlying lymphoproliferative, or plasma cell disorder **Table 3**.[4,13-71] The remaining 31 cases include clofazimine-related CSH (four cases), associated with other hematologic-related diseases (two cases: plasma cell granuloma and systemic mastocytosis), or without evidence of association with any other diseases.[1-3,5-11,57,72-90] The average age of patients with CSH and an underlying lymphoproliferative or plasma cell disorder is 60 years (range, 18-91 years) with a nearly equal male:female distribution (51:45) (three cases unknown). BM was the most common site of involvement, followed by lung/pleura, kidney, lymph node, gastrointestinal tract, head, and neck. Most cases (82%) had only one confirmed site of involvement **Table 4**. The average age of patients with CSH without an underlying lymphoproliferative or plasma cell disorder is 54 years (range, 19-80 years) with a nearly equal

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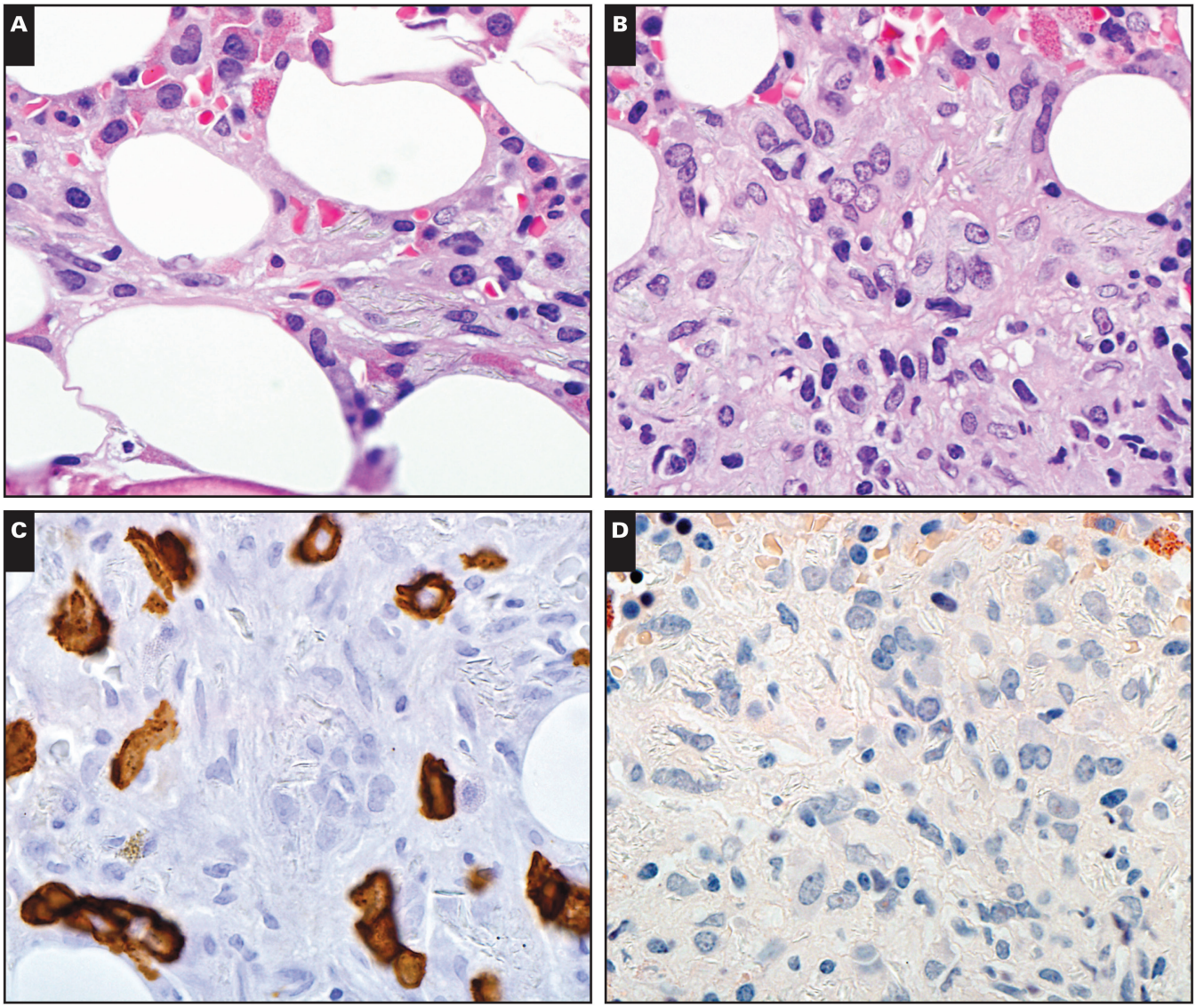

Image 5 Crystal-storing histicocytosis associated with foreign body granuloma. In the bone marrow core biopsy, the histiocytes form a granuloma with refractory elongated crystals (**A**, H&E, x1,000), or multinucleated giant cell (**B**, H&E, x1,000). CD138-positive plasma cells encircle the outer rim of the granulomas (**C**), while Congo red nicely demonstrates the negatively staining crystalline inclusions in the histiocytes and multinucleated giant cell (**D**, x1,000).

male:female distribution of 14:16 (two cases unknown). Of the BM-CSH cases specifically, the average age of diagnosis is 62 years (range, 35-79 years) with a male predominance (male:female 26:11) (three cases unknown).

Discussion

BM-CSH is an exceedingly uncommon phenomenon accounting for less than 1% of all BM cases reviewed at our institution over a 5-year period. This may be an underrecognized phenomenon due to occasional subtle histiocytic infiltrates. In keeping with previously published reports,[4,57] our study shows that BM-CSH is most often associated with a plasma cell neoplasm and essentially all cases involve a κ light chain monoclonal protein without specific heavy chain association. Similar to the observation by Jones et al,[57] we also noted persistent CSH after chemotherapy or BM transplant. In our study, no significant differences on clinical outcome were observed between localized and generalized CSH.

BM-CSH displays strikingly variable histologic appearances with regards to the crystalline appearance, cytoplasmic quality, and histiocytic distribution. The crystalline inclusions in histiocytes range from needle-like, globular, to hexagonal with variability often

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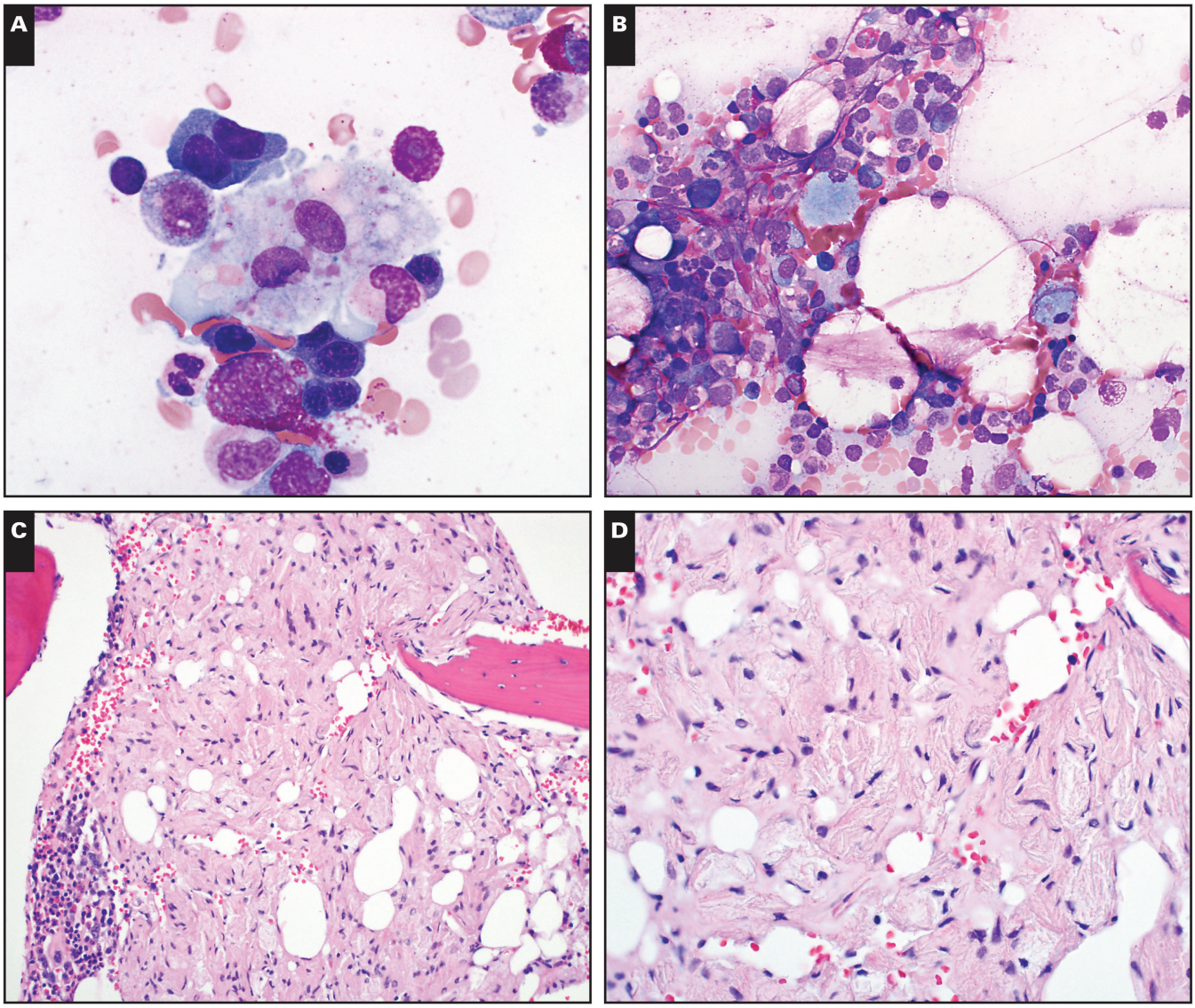

Image 6 Crystal-storing histiocytosis associated with plasma cell myeloma. The histiocyte cytoplasm was pale with light-colored globules (**A**, Wright-Giemsa, x1,000), or occasional Gaucher-like forms (**B**, Wright-Giemsa, x600). In the biopsy, the histiocytes showed epithelioid granuloma-like distribution (**C**, H&E, x600) and were Gaucher-like with striated cytoplasm (**D**, H&E, x1,000).

occurring within the same case (Images 1-6). The cytoplasmic appearance of involved histiocytes is also notably variable ranging from bland/lightly azurophilic to brightly eosinophilic, globular-like, subtly granular, striated, and even Pseudo-Gaucher-like (Images 1-6). When associated with a clonal plasma cell process, the plasma cells in CSH, in addition to the histiocytes, may also contain cytoplasmic crystals (APL cell-like, or globule-like, or numerous small chunky granules). Based on our case series, the histiocytic infiltrates ranged from less than 10% to over 30% of BM cellularity, with the distribution patterns varying from interstitial to granuloma-like, clusters, or loose aggregates.

Given the diverse appearances of the histiocytes and their infiltration patterns in BM-CSH, careful consideration and evaluation for other potential entities are needed to avoid misinterpretation. Potential morphologic mimickers of CSH in the BM include Gaucher disease (Image 6) or other storage disorders, infectious disease/granulomatous inflammation (Images 2, 5, and 6), hemophagocytic lymphohistiocytosis, and megakaryocytic dysplasia (Image 2). Similarly, pathologists should be aware that an underlying plasma cell neoplasm or B-cell lymphoma could be masked by the histiocytic infiltrates. For example, in case 4, the histiocytic infiltrate was significantly prominent and the relative smaller proportion of clonal plasma cells corresponding to PCM could have been overlooked.

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Table 2
Pathological Characteristics of Eight Cases of BM-CSH

Case No.	Cytoplasmic Characteristics of Histiocytes in Aspirate	Crystal Appearance in Aspirate	% Histiocytes in Biopsy	Distribution Pattern of Histiocytes in Core Biopsy	Cytology of Histiocytes in Biopsy	% BM by Underlying Neoplasm	Cytogenetics	FISH (Plasma-Cell Related)
1	Light blue	Needle-like or globular	10-30	Interstitial	Lightly eosinophilic	20	Normal	Normal
2	Sea blue or megakaryocyte-like	Globular	30	Granuloma-like	Pink smooth cytoplasm	20	Normal	Positive for *CCND1/IGH* fusion
3	Eosinophilic	Needle-like or globular	10-30	Loose aggregates	Gaucher-like; striated	60	Normal	+3, +9, +11, +15
4	Globular or light azurophilic	Needle-like	>30	Aggregates	Pink cytoplasm with hexagonal crystals or Hürthle cell-like	10	Normal	+7, +9, +13, t(*IGH*)
5	Suboptimal specimen	Suboptimal specimen	<10	Granuloma-like	Needle-like crystal inclusions	<5	NA	NA
6	Pseudo-Gaucher	Globular	<10	Epithelioid granuloma-like	Gaucher-like; striated	20	Normal	Negative for t(11;14), t(4;14), t(14;16), del (1p), +1q, -13/del (13q), or del (17p)
7	Sea blue	Needle-like	>30	Granuloma-like	Large crystals and multinucleated giant cells	5	Normal	NA
8	Granular	Needle-like	<10	Interstitial	Pink smooth cytoplasm	30	Normal	Positive for *CCND1/IGH* fusion

BM, bone marrow; CSH, crystal-storing histiocytosis; FISH, fluorescence in situ hybridization; NA, not available.

The morphologic similarities of CSH with other entities such as Gaucher disease and rhabdomyoma have also been noted by others in the literature. Several studies have elegantly illustrated that pseudo-Gaucher histiocytes in CSH cases resemble true Gaucher disease.[3,48,91] In such situations, iron staining may be a useful method for its diagnosis because pseudo-Gaucher histiocytes are mostly negative for iron staining.[92] The occasional CSH case that may show positive iron staining in histiocytes should not, however, be misinterpreted as Gaucher disease. The unique heterogeneous iron staining pattern, with unstained crystals standing out against a background of strong stained histiocytes, can provide an important feature for the diagnosis of CSH.[27] Similar to Gaucher disease, several research groups have also reported CSH cases mimicking adult rhabdomyoma.[47,49,58] These two entities share similarities in morphology both described as large plump cells with bland oval nuclei and striated, eosinophilic cytoplasm. However, the histiocytes in CSH, in contrast to rhabdomyoma tumor cells, are positive for CD68 and negative for smooth muscle markers. In these reports, the authors suggest that in the case of adult rhabdomyoma with atypical histologic findings, CSH should be considered and ruled out to prevent a serious misdiagnosis.[47,49,58] Typical locations of adult rhabdomyoma would include the mucosal surface of the oral cavity, larynx and pharynx, and the soft tissues of the neck.

CSH occurs most often in association with an underlying clonal plasma cell or B-cell disorder (76% in our study to 90% in the literature).[1] The slight variation in the percentage of reported cases may stem from increased recognition of this rare entity in recent years. Jones et al[57]suggested that Ig crystal formation by plasma cells was frequently associated with the proliferations of crystal-laden histiocytes. Recent mass spectrometry series[4] confirmed that the histiocytes contained Ig fragments, likely derived from lymphoma or neoplastic plasma cells. The most common non-Ig related CSH was clofazimine crystals found in lepromatous leprosy patients.[5-8] The

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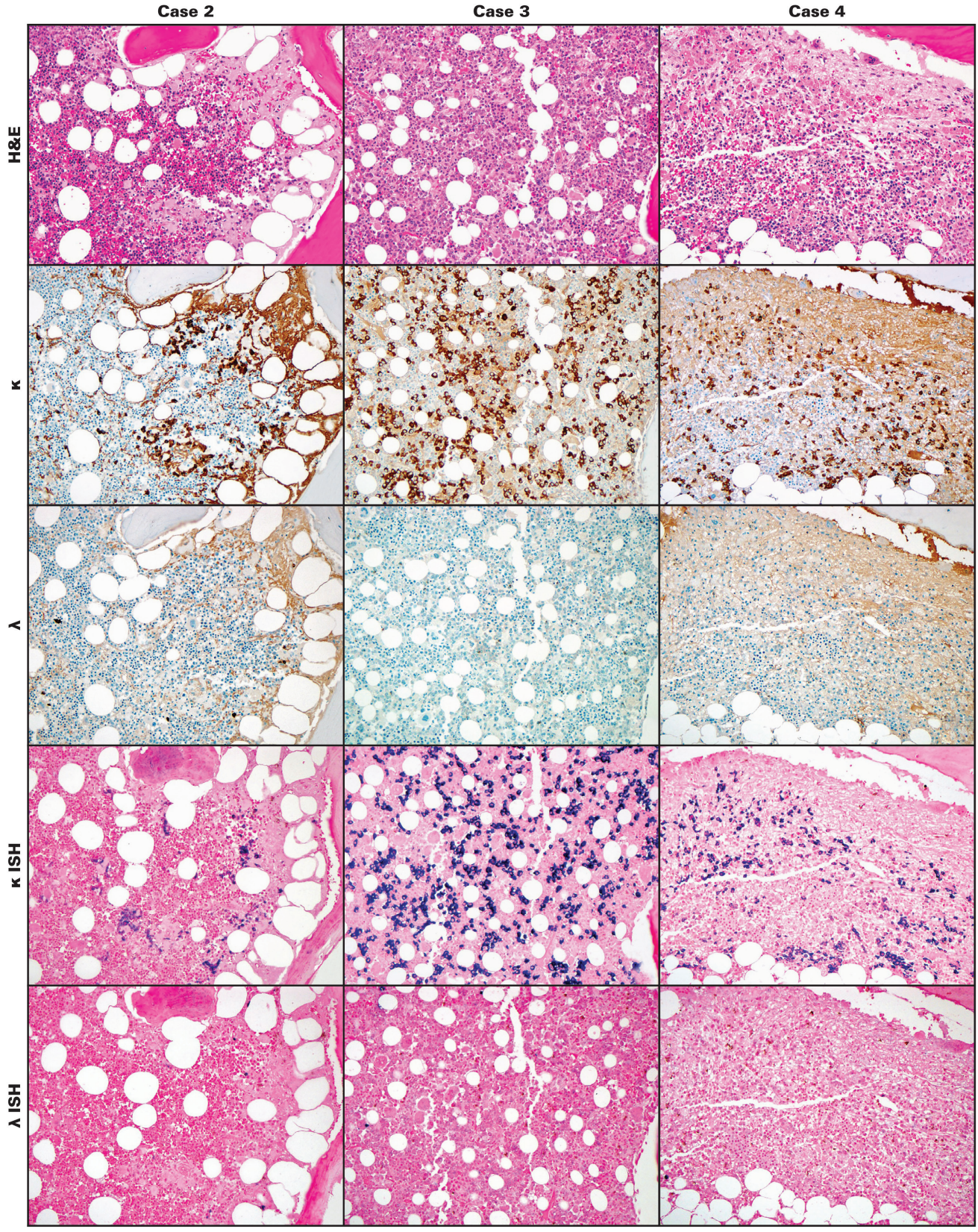

Image 7 Immunohistochemical and in situ hybridization (ISH) stains for κ and λ in crystal-storing histiocytosis involved with bone marrow. Cases 2 to 4 highlighted the clonal (κ) plasma cell infiltrates and did not reveal any significant perceptible differences between an immunohistochemical staining technique and ISH (x200).

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review by Sukpanichnant et al[7] described additional 14 cases of clofazimine-induced CSH, which were not included in the literature review. Similar to case 2 in our series, Balakrishna's group reported a CSH case with amyloidal deposition.[11]

In a review of the literature of all CSH cases published since 1987 (Table 4), it is interesting that the largest number of localized and generalized CSH cases, by site, involve the BM (22% and 70%, respectively). Importantly, as a whole, localized CSH cases far outnumber generalized cases (82% vs 18%; Table 4). Focusing specifically on BM-CSH cases (Table 5), there is a trend of male predominance (26 males vs 11 females), while the CSH cases with other sites of involvement had relatively equal distribution (39 males vs 50 females). Similar to CSH cases as a whole, the majority of BM-CSH cases (38/40, 95%) had an underlying lymphoproliferative or plasma cell disorder (29 plasma cell dyscrasia/neoplasm, two B-cell lymphoma, and seven lymphoplasmacytic lymphoma). The remaining two cases were Fanconi syndrome and systemic mastocytosis. Not surprisingly, the monoclonal spikes in these cases were mostly with κ light chain restriction (28/30, 93%) and a mixed distribution of heavy chains including IgG (16/28, 57%), IgA (8/28, 29%), and IgM (4/28, 14%).

In our case series, we also identified a foreign body granuloma-associated CSH (Image 5), which, to our best knowledge, has never been reported previously. This case had a clinical history of meperidine injection and presented with crystalline materials in histiocytes in multiple sites including skin and liver. Subsequent ultrastructural spectral analyses determined the crystals contained silicone, magnesium, and oxygen, suggesting a silicate. Due to the presence of an IgG κ paraprotein, the patient underwent a BM biopsy, which showed small granulomata and foci of crystal-laden histiocytes with κ light chain–restricted plasma cells in the vicinity of these cells. Although mass spectrometry was not performed in order to confirm an Ig-related

Table 3
Underlying Diagnosis in 131 Cases of CSH Reported in the English Literature From 1987 to 2017 (Including the Current Study)

Underlying Diagnosis	No. of Cases (%)
CSH with underlying LP-PCD	100 (76%)
Plasma cell myeloma	24
Lymphoplasmacytic lymphoma	15
MGUS	13
Plasma cell dyscrasia/neoplasm	13
B-cell lymphomafurther subclassified as	35
MALT lymphoma	24
B-cell lymphoma, not classified	7
Nodal MZL	2
Splenic MZL	2
CSH without underlying LP-PCD	31 (24%)

CSH, crystal-storing histiocytosis; LP-PCD, lymphoproliferative or plasma cell disorder; MALT, mucosa-associated lymphoid tissue; MGUS, monoclonal gammopathy of undetermined significance; MZL, marginal zone lymphoma.

Table 4
Localized and Generalized CSH Cases: Site(s) of Disease as Reported in the English Literature from 1987 to 2017 (Including the Current Study)

Site	Localized CSH (Single Site, n = 108)	Generalized CSH (Multiple Site, n = 23)	Total (n = 131)
Bone marrow	24 (22%)	16 (70%)	40 (31%)
Lung and pleura	19 (17%)	1 (5%)	20 (15%)
Kidney	14 (13%)	5 (24%)	19 (15%)
Lymph node	6 (6%)	8 (38%)	14 (11%)
Gastrointestinal tract	9 (8%)	5 (24%)	14 (11%)
Head and neck	9 (8%)	4 (19%)	13 (10%)
Eye/orbit	6 (6%)	2 (10%)	8 (6%)
Skin	6 (6%)	2 (10%)	8 (6%)
Central nervous system	6 (6%)	0	6 (5%)
Breast	4 (4%)	1 (5%)	5 (4%)
Liver	0	4 (19%)	4 (3%)
Spleen	1 (1%)	2 (10%)	3 (2%)
Body fluid	2 (2%)	0	2 (2%)
Upper back/arm	0	2 (10%)	2 (2%)
Heart	1 (1%)	0	1 (1%)
Soft tissue	1 (1%)	0	1 (1%)
Thymus	0	1 (5%)	1 (1%)
Esophagus	0	1 (5%)	1 (1%)
Peritoneum	0	1 (5%)	1 (1%)
Omentum	0	1 (5%)	1 (1%)

CSH, crystal-storing histiocytosis.

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Table 5
Summary of BM-CSH Reported in the English Literature from 1987 to 2017 (Including the Current Study)

Author (Year)	No. of BM-CSH Cases	Male/Female	Underlying Diagnosis (PCN/B-Cell Lymphoma/LPL)	M-Spike (Heavy Chain/Light Chain)	No. of Localized/ Generalized CSH Cases
Takahashi et al[67] (1987)	1	Unknown	1/0/0	IgA κ	1/0
Jones et al[57] (1999)	10	7/3	5/0/5	IgA (2/6); IgM (1/6); IgG (1/6); biclonal (2/6); κ (3/4); λ (1/4)	5/5
Lebeau et al[60] (2002)	1	1/0	1/0/0	IgA κ	1/0
Papla et al[62] (2004)	1	1/0	1/0/0	IgG κ	0/1
Zioni et al[71] (2004)	1	Unknown	1/0/0	Unknown	1/0
de Lastours et al[37] (2006)	2	1/1	2/0/0	IgG (1/2); IgA (1/2); κ (2/2)	0/2
Keane and Gill[42] (2008)	1	1/0	1/0/0	Unknown/κ	1/0
Kar et al[41] (2008)	1	1/0	1/0/0	IgG κ	1/0
Farooq et al[38] (2009)	1	1/0	1/0/0	IgG κ	0/1
Alayed et al[9] (2010)	1	Unknown	0/0/0[a]	Unknown	1/0
Park et al[48] (2010)	1	1/0	1/0/0	No apparent monoclonal protein/κ	1/0
Hu et al[26] (2012)	1	0/1	1/0/0	IgG κ	1/0
Duquesne et al[2] (2013)	1	0/1	0/0/0[b]	IgG κ	0/1
Miura et al[27] (2013)	1	0/1	1/0/0	No apparent monoclonal protein	1/0
Lee et al[19] (2015)	1	0/1	1/0/0	IgA κ	1/0
Baird et al[18] (2015)	1	0/1	0/0/1	IgM λ	0/1
Aline-Fardin et al[17] (2015)	1	1/0	0/1/0	IgG κ	0/1
Kanagal-Shamanna et al[4] (2016)	4	3/1	3/0/1	IgG (2/4); IgA (1/4); IgM (1/4); κ (4/4)	3/1
Uthamalingam and Mehta[14] (2017)	1	1/0	1/0/0	IgG/κ	1/0
Current study	8	7/1	7[c]/1/0	IgG (5/7); IgA (1/7); IgM (1/7); κ (7/7)	5/3

BM, bone marrow; CSH, crystal-storing histiocytosis; Ig, immunoglobulin; LPL, lymphoplasmacytic lymphoma; PCN, plasma cell dyscrasia/neoplasm.
[a]Systemic mastocytosis.
[b]Fanconi syndrome.
[c]One case with systemic amyloidosis with myeloma.

CSH in BM, clinically there were features to suggest both κ light chain–related CSH and a foreign body granuloma-associated CSH.

In summary, we report eight cases of BM-CSH in conjunction with a review of the published literature. This study identifies and confirms the unique nature of this disorder in the bone marrow. BM-CSH appears to be quite a rare entity overall, has a clear-cut association with an underlying clonal disorder involving plasma cells, is strongly associated with κ light chain monoclonal protein, is less commonly composed of nonimmunoglobulin crystals, and may, on occasion, exhibit a morphologic appearance that could be initially mistaken for an alternative disorder. Given that BM-CSH is an uncommon phenomenon, we speculate if it is possibly also underrecognized due to resemblance to other entities. BM-CSH exhibits a wide morphologic spectrum with respect to the appearance of histiocytes and crystals. Importantly, given that this is an uncommon finding, careful evaluation and exclusion of potential mimickers such as dysplastic megakaryocytes and granulomatous inflammation is essential. Awareness of the morphologic diversity of CSH will enable recognition of this entity and reaching the correct diagnosis. Early detection of CSH could be the first clue to unveiling the presence of an underlying clonal plasma cell or B-cell disorder and will optimize patient diagnosis and management.

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