Annals of Diagnostic Pathology 40 (2019) 13–17

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Review Article

Crystal storing histiocytosis: Unusual clinical presentations in two patients

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1. Introduction

Crystal-storing histiocytosis (CSH) is a rare entity that may precede or occur in conjunction with an underlying disorder. It is characterized by the presence of crystal laden histiocytes and most often associated with a monoclonal gammopathy secondary to lymphoma, multiple myeloma or leukemia. However, there are rare reports of CSH associated with Clofazimine use, silica exposure and hereditary cystinosis without an underlying lymphoproliferative disorder or plasma cell dyscrasia [1]. The immunoglobulin crystals of CSH are usually kappa restricted, although there are case reports with lambda and polyclonal crystal formation [1,2]. While CSH has a varied clinical presentation, certain histologic features, though sometimes subtle, are constant between cases and allow recognition of this distinctive entity, thereby providing the basis for investigation of underlying diseases or associations. Herein we discuss two cases with diverse presentations of clinically unsuspected CSH.

2. Materials and methods

2.1. Histopathology and immunohistochemistry

All surgical pathology specimens were fixed in 10% buffered formalin, embedded in paraffin and sectioned at 4 μm. The tissue was then stained with hematoxylin and eosin.

Immunohistochemical analysis was performed with the appropriate reactive controls for each case received in consultation. Immunohistochemical stains performed on the specimen from patient 1 include: CK7, CK20, AE1/AE3, CD68, Kappa, Lambda, smooth muscle actin (SMA), epithelial membrane antigen (EMA), CD117, HMB45, SOX10, Calretinin, and PAS. Immunohistochemical stains performed on the specimens from patient 2 include: AE1/AE3, C34, CD68, CD117, CD138, S100 protein, ALK-1, SMA, and Desmin.

2.2. Case 1

The first patient, a 68-year-old woman, presented with occasional dyspnea, increasing fatigue and a remote history of pneumonia. She was found to have a right pleural density of uncertain etiology on chest CT with contrast. The lesion was extrapulmonary, 4.7 cm in greatest dimension and merged with the paraspinous soft tissues without evidence of bone invasion. The patient's review of systems was negative for fever, chills, weight loss, cough or dizziness. She had a history of hypothyroidism and had never smoked. Physical exam was unremarkable.

The extrapulmonary lesion was biopsied. In routinely stained H & E sections, the lesion comprised of sheets of epithelioid to spindled histiocytes with eccentrically placed, hyperchromatic nuclei and occasional, inconspicuous nucleoli. The cytoplasm of these histiocytes was brightly eosinophilic and on high magnification appeared to contain crystals which were needle-like to rhomboid and did not polarize. In addition, there were aggregates of lymphocytes and plasma cells without cytological atypia throughout the lesion, particularly in a perivascular pattern.

Immunohistochemistry was performed and the histiocytes were strongly and diffusely positive for CD68 and kappa light chain, while they were negative for lambda light chain, cytokeratins AE1/AE3, CK7, CK20, SMA, EMA, CD117, HMB45, SOX-10, calretinin and periodic acid Schiff (PAS) staining. The positive and negative immunohistochemistry in conjunction with the classic histology of non-malignant histiocytes with intracytoplasmic, crystalline inclusions led to a diagnosis of CSH (Fig. 1). Further evaluation of the patient for a possible underlying lymphoproliferative disorder or plasma cell dyscrasia was suggested. Prior to discharge the patient was found to have an M spike in her serum of 0.4 g/dL and free kappa light chains within the urine at 24 mg/L. She was advised to see an oncologist and have repeat studies performed; however, the patient refused and has been subsequently lost to follow-up.

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https://doi.org/10.1016/j.anndiagpath.2019.01.003

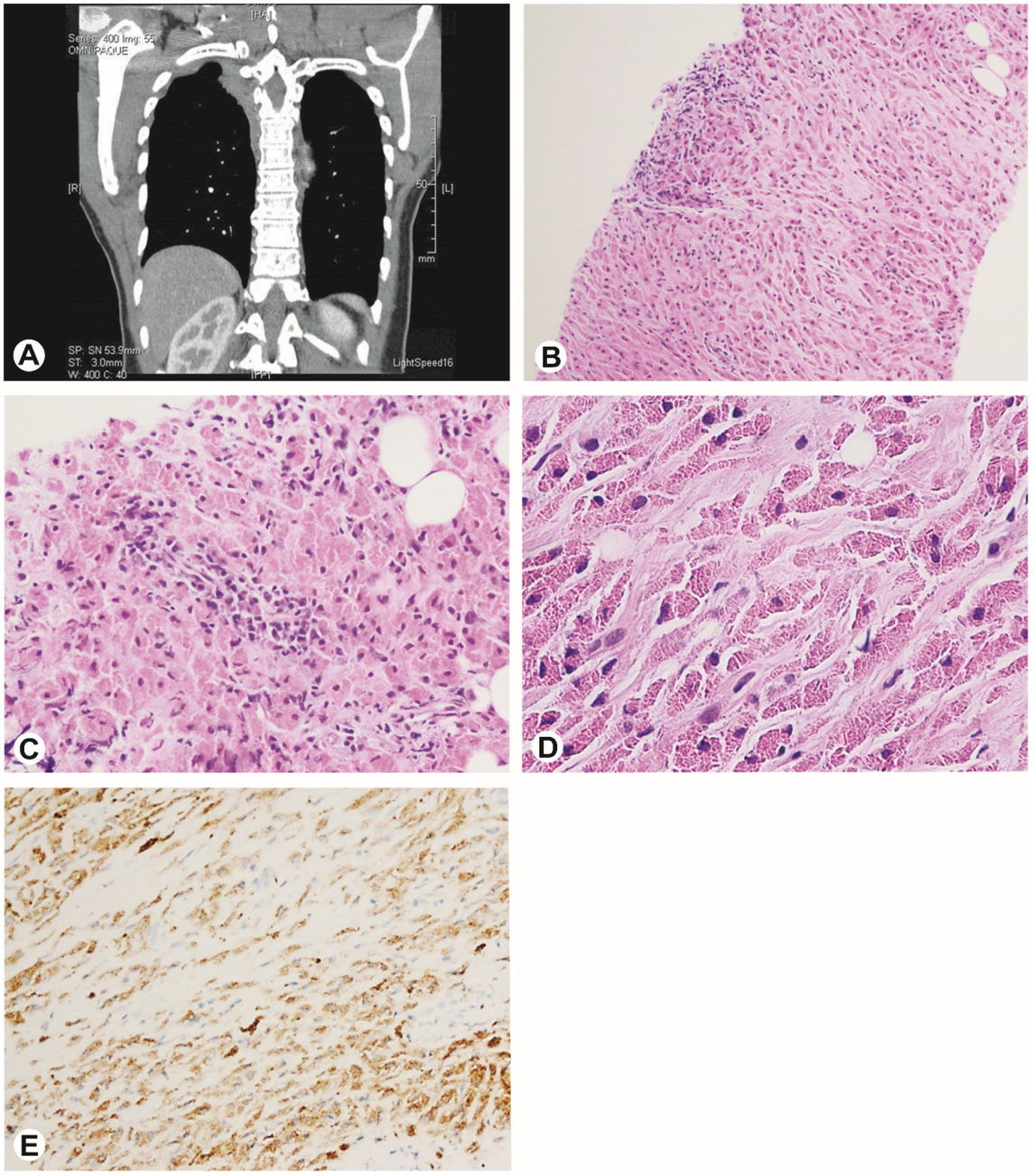

Fig. 1. Biopsy of pleural lesions of patient 1 (Print in Color)
A. CT with contrast demonstrates a marginated, 8 cm long, extrapulmonary paraspinal mass primarily adjacent to the T4 and T5 vertebrae. The mass blends with the pleural thickening in the area with no destructive bone changes identified. B. Proliferation of cells with deeply eosinophilic cytoplasm, eccentrically placed and hyperchromatic nuclei with no obvious nucleoli. No mitosis or necrosis are present. C. Other foci of the biopsy demonstrate clusters of plasma cells and lymphocytes, particularly around the blood vessels. The cells contained no abnormal nuclear features. D. At a higher magnification the cells contain rhomboid, needle shaped crystals, which are non-birefringent. E. Immunohistochemical stains for CD68 were diffusely positive within the crystal containing cells of interest. B-D, hematoxylin and eosin stain; E, CD68 immunohistochemical stain. B, 10×; C and E, 20×; D, 40×.

2.3. Case 2

The second patient, a 49-year-old male, was admitted to the hospital with a history of progressive weight loss, an inability to eat, burning upper abdominal pain and weakness. He had a recent history of an open cholecystectomy but no other past medical history was reported. Laboratory data was within normal limits on presentation with the exception of mild anemia. The patient's physical exam was significant for cachexia, a healing scar in the subcostal region, and tenderness to palpation with a mass in the epigastric area. Due to a concern for an underlying gastric malignancy, the patient underwent endoscopy. On endoscopy, no mucosal malignancy was identified; however, evaluation by CT scan showed a thickened gastric wall with concern for lymphoma or some type of gastrointestinal stromal tumor.

Therefore, the patient underwent an exploratory laparotomy with lysis of adhesions. Within the peritoneum, an intense inflammatory response was noted originating from the stomach. The lesser omentum was creeping onto the stomach itself and the stomach was thickened to palpation from the antrum all the way to the fundus. A large biopsy of the antrum (> 1 cm in thickness) was taken with several others including omentum and sent for frozen section with a preliminary diagnosis of no definitive malignancy, pending permanent sections.

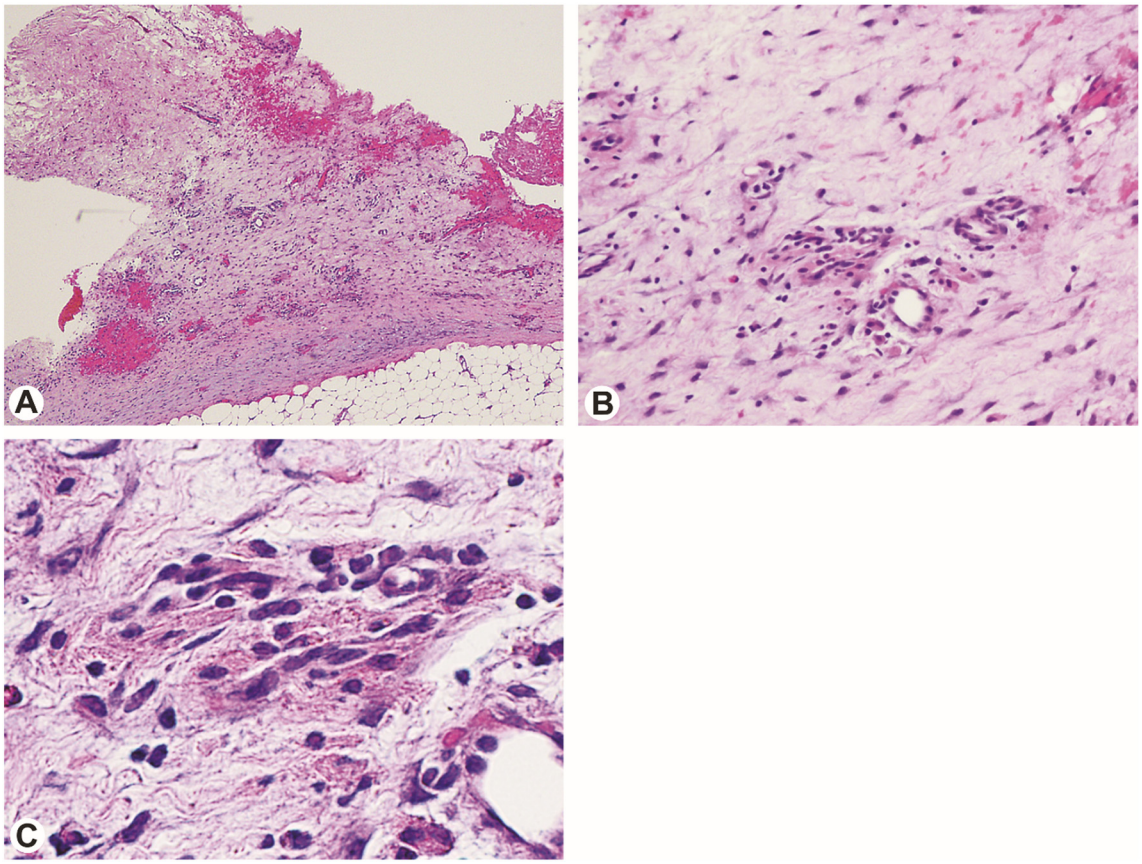

Fig. 2. Biopsy of abdominal wall lesion for patient 2 (Print in Color)
A. Cellular and fibrotic biopsy of the abdominal wall demonstrating aggregates of eosinophilic, epithelioid to spindled cells, particularly around the blood vessels. B. Spindle cells with eccentrically placed nuclei, occasional nucleoli, mild pleomorphism, and densely eosinophilic cytoplasm make up the aggregates seen at lower power. C. Needle like crystalline structures are found within the eosinophilic cytoplasm of the spindled cells. A–C hematoxylin and eosin stain. A, 4×; B, 20×; C, 60×.

On histologic examination, all areas showed similar features including a diffuse proliferation of bland spindle cells involving the serosa, muscularis propria and the submucosa. The cells contained small, hyperchromatic nuclei with finely clumped chromatin and several possessed a single small nucleolus. The cytoplasm of the cells was pale and eosinophilic with mild cellular pleomorphism and very little mitotic activity. In addition, there were areas of perivascular hypercellularity with a mixed inflammatory infiltrate consisting of lymphocytes, polymorphonuclear leukocytes and many eosinophils. (Fig. 2)

Immunohistochemical studies revealed the lesion was negative for CD34, CD117, S100 protein and ALK-1. SMA was interpreted as positive in the spindle cells and non-specific perinuclear, patchy positivity for desmin and cytokeratins AE1/AE3 was noted. The patient was diagnosed with mesenteric and retroperitoneal fibromatosis. An outside consultative opinion was obtained at that time and a reactive myofibroblastic process was favored although an inflammatory myofibroblastic tumor had also been considered.

The patient continued to have pain and his health deteriorated. Two years after the exploratory laparotomy, he presented with a compression fracture of the lumbar spine. Bone marrow biopsy performed at that time demonstrated a florid proliferation of epithelioid to spindled histiocytes with brightly eosinophilic, intracytoplasmic crystalline inclusions replacing the marrow space. The histiocytes were diffusely and strongly positive with CD68. In addition, there were occasional CD138 positive plasma cells with kappa light chain restriction. The patient was ultimately diagnosed with CSH-associated plasma cell myeloma and prominent multifocal fibrosclerosis. He succumbed to disease within 2 months of diagnosis. (Fig. 3)

3. Discussion

Crystal-storing histiocytosis (CSH) is a rare entity with less than 100 cases reported in the literature. Although awareness of CSH among pathologists and clinicians is gradually increasing, lack of familiarity with CSH as an entity and the characteristic appearance of its crystal-laden histiocytes are the primary reasons pathologists fail to make the diagnosis.

CSH is often reported in middle to older aged adults with an equal distribution between males and females. The exception is CSH associated with autoimmune diseases, which have a female predominance [1,3]. Disease presentation is variable with many patients showing localized, asymptomatic masses or swellings. Dogan et al. reviewed the literature of 80 cases of immunoglobulin associated CSH; 46 of these patients presented with localized disease with the most common location being the head and neck region in 35% of patients followed by the lung and pleura in 24%. Generalized forms of CSH involve the bone marrow, lymph nodes, liver and spleen in descending order of frequency. Generally, patients are asymptomatic and incidental masses are identified. However, if symptoms are present, they tend to be specific for the site of presentation. For instance, a 64-year-old man presented with a prior history of weakness, supraventricular tachycardia and an atrial mass, which on biopsy proved to be CSH [4]. Rossi et al. reported five cases of pleuropulmonary CSH with a range of symptoms including chest pain with hemoptysis to fever and dyspnea [2].

CSH in and of itself is not a malignant process but > 90% of cases are associated with a hematologic malignancy including lymphoplasmacytic lymphoma, chronic lymphocytic leukemia, extranodal

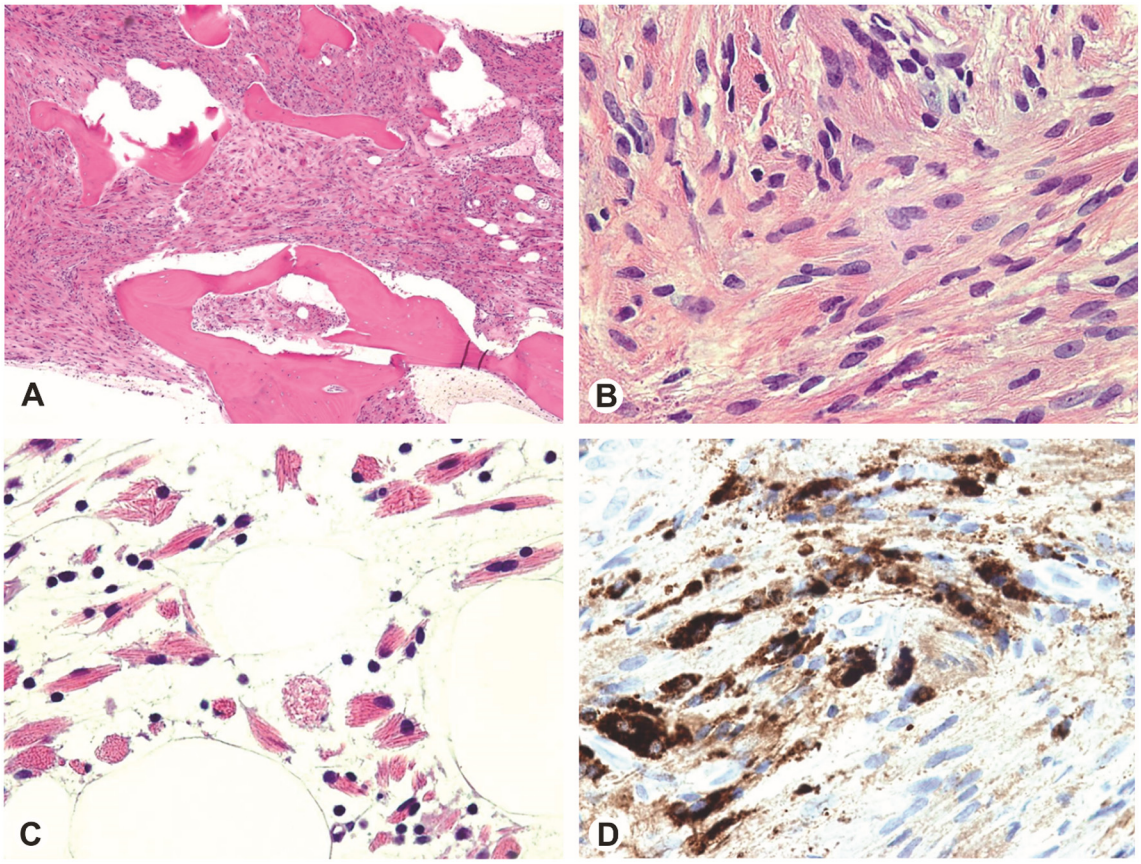

Fig. 3. Bone marrow biopsy of patient 2 (Print in Color)
A. The marrow space is replaced with deeply eosinophilic cells and fibrosis. B and C. On higher magnification the spindled histiocytes contain brightly eosinophilic, needle-shaped crystals with a loss of normal marrow components. D. The histiocytes stain strongly positive for CD68. A-C, hematoxylin and eosin stain. D, CD68 immunohistochemical stain. A, 2×; B & D, 40×; C, 60×.

marginal zone lymphoma, plasma cell myeloma and systemic mastocytosis. Therefore, identification of CSH on biopsy should prompt the clinician to investigate whether an underlying disorder is present and if not identified, active surveillance should be pursued. Other diseases that CSH has been associated with include rheumatoid arthritis, Crohn's disease and administration of Clofazimine, an antibiotic traditionally used to treat leprosy. [1,2,5-8]

Despite the varied presentations and disease associations, certain histologic features of CSH remain constant, albeit subtle at times. In routinely stained hematoxylin–and-eosin stained sections, CSH presents with sheets of polygonal and occasionally spindle shaped histiocytes with eccentrically placed, hyperchromatic nuclei with fine chromatin. There may be occasional, inconspicuous nucleoli but no mitoses, significant pleomorphism or necrosis should be present. The cytoplasm of the histiocytes is characteristically deeply eosinophilic and opaque, which often times obscures the intracytoplasmic crystals and renders diagnosis difficult. On close examination or occasionally with polarization, the cytoplasm of the histiocytes will contain needle-like to rhomboid shaped crystals. The background may contain aggregates or sheets of lymphocytes and plasma cells, which may be clonal if CSH is associated with a lymphoproliferative disorder. One pitfall in diagnosis is that the predominance of histiocytes may mask an underlying lymphoproliferative disorder. Additionally, the lesions of CSH are often poorly circumscribed and may contain other cell types including scattered giant cells. [1,3]

Immunohistochemistry studies demonstrate that the crystal-laden histiocytes are diffusely positive for CD68 and negative for desmin, myoglobin, S100 protein, CD1a, vimentin, and cytokeratins. They are variably positive or negative for PAS. The intracytoplasmic crystals stain positively and monotypically for kappa or lambda in most instances or for heavy chains, although they may occasionally be polyclonal. In addition, the crystals are reported to stain blue with phosphotungstic acid hematoxylin [1,9].

Performing the aforementioned immunohistochemistry studies is extremely important in excluding other diseases which may simulate CSH, including but not limited to adult rhabdomyoma, granular cell tumor, Langerhans cell histiocytosis, Rosai Dorfman disease and pseudo-Gaucher's crystals of chronic myelogenous leukemia [1,5]. Adult rhabdomyoma, like CSH, contains brightly eosinophilic epithelioid and spindled cells that may contain focal intracytoplasmic crystals as well as striations, which represent hypertrophic Z bands. This tumor, in contrast to CSH, will be positive for muscle specific markers including desmin, myoglobin and muscle specific actin [10]. Granular cell tumors will have eosinophilic, epithelioid cells somewhat similar to those seen in CSH; however, the cytoplasm will contain granules rather than crystals. In addition, this tumor will be positive for S100 protein in contradistinction to CSH. [1,11,12]

Langerhans cell histiocytosis (LCH) should be distinguishable from CSH morphologically by folded/grooved nuclei and the presence of eosinophils amongst the histiocytes. Again, should immunohistochemistry be needed, the lesional cells of LCH will also be positive for CD1a and Langerin, while CSH will be negative. Rosai Dorfman disease of soft tissue is another predominantly histiocytic entity that could be confused with CSH, particularly in view of comingled lymphocytic and plasmacytic components, but the presence of emperipolesis and S100 protein positive histiocytes of RDD serve to distinguish the two. Lastly, the pseudo- Gaucher cells of chronic myelogenous leukemia can present a diagnostic dilemma given the

association with a hematologic malignancy and intracytoplasmic, eosinophilic inclusions. What distinguishes this entity from CSH is that the intracytoplasmic material is an accumulation of not only immunoglobulins but cellular debris from the proliferating neoplasm. This can be distinguished morphologically, by electron microscopy and at times by immunohistochemistry demonstrating a lack of immunoglobulin restriction. [1,4]

The crystals of CSH are most commonly located within histiocytes but they have also been reported in endothelial cells, renal tubular epithelial cells, particularly in patients with Fanconi's disease, and neoplastic plasma cells [3]. Most commonly the crystals comprise monoclonal immunoglobulin kappa (κ) light chains. Little is known of the molecular data and underlying mechanisms of light chain crystal formation and their storage in the macrophages of CSH. The detection of amino acid substitutions and certain structural features in the κ light chain variable sequences have led to suggestions that they produce structural changes that could play a role in crystal deposition [13,14]. However, a more recent report found no mutations in the κ light chains and suggested that intrinsic properties of κ light chains may predispose to their intralysosomal accumulation, resistance to lysis, and propensity to form crystals. [15]

In summary, we have presented two cases that demonstrate the classic histomorphology of CSH and the importance of keeping this entity in the differential diagnosis. Of note, the second patient had been briefly described in a series of 13 previously reported cases [8]. Nevertheless, we included this extremely difficult case in our discussion of CSH because the intra-abdominal biopsies were shown to one of us in consultation when the patient re-presented with bone marrow involvement, which showed florid CSH. The findings in the intra-abdominal biopsies and subsequent gastric mucosal biopsies were distinctly more nuanced than those in the bone marrow due to prominent background fibrosis and spindling of histiocytes misconstrued as fibroblasts, thereby leading to a delay in diagnosis and treatment for at least 2 years. As illustrated in this case, CSH may present with symptoms mimicking malignancies such as mesothelioma or carcinomatosis or it may be unassociated with symptoms. Therefore, knowing the histology and the immunohistochemistry, particularly when ruling out common mimickers, can lead to the correct diagnosis and ultimately to the investigation of an underlying hematologic malignancy, autoimmune disorder or infection.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors.

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