Nodular Histiocytic/Mesothelial Hyperplasia Mimicking Mesenteric Metastasis

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Abstract

Nodular histiocytic/mesothelial hyperplasia (NHMH) is a rare histologic entity, characterized by localized benign reactive proliferation of histiocytes and mesothelial cells. The presence of this rare entity poses a challenge in differential diagnosis, both in radiological findings and pathological interpretations under certain circumstances, and consequently has been misdiagnosed as malignancy. Here, we report a case of mesenteric NHMH in a patient with colonic mucinous adenocarcinoma. Histology shows numerous large calretinin (+) mesothelial cells mixed with CD68 (+) histiocytes by immunohistochemistry. In contrast to almost all previously reported cases with typical features of histiocytic predominance, the current case of NHMH mainly consists of mesothelial cells with intermixed histiocytes. The findings expand the histologic spectrum of NHMH and contribute to awareness of this entity in the differential diagnosis.

Introduction

Nodular histiocytic/mesothelial hyperplasia (NHMH) is a rare benign tumor-like lesion characterized histologically by the localized reactive proliferation of histiocytes and mesothelial cells [1]. This lesion may occur at various sites of the body, predominantly mesothelium-lined locations, such as pleura, pericardium, and peritoneum, and rarely non-mesothelium-lined locations such as the endocardium and aortic dissecting aneurysms [2-4]. Less than 100 cases have been reported in the literature thus far. The main clinical significance for this entity is the challenging differential diagnosis under circumstances, such as metastatic adenocarcinoma, clear cell carcinoma of the lung, primary mesothelioma, Rosai-Dorfman disease, serous carcinoma, and Langerhans cell histiocytosis of the pleura, pericardium, cardiac valves, peritoneum, pelvis, and groin [2,5-7]. Here, we report a case of mesenteric NHMH in a patient with colonic adenocarcinoma clinically mimicking mesenteric metastasis. Histology shows numerous large calretinin (+) mesothelial cells mixed with CD68 (+) histiocytes by immunohistochemistry. In contrast to almost all previously reported cases with typical features of histiocytic predominance [1-2,4-5,7-9], the current case of NHMH mainly consists of mesothelial cells with scattered histiocytes. The findings expand the histologic spectrum of NHMH and raise awareness of histologic variation in this rare entity.

Case Presentation

An 87-year-old male with a past medical history of hypertension and hyperlipidemia presented to the hospital due to scalp laceration and cerebral concussion following a fall at home. On admission, a workup showed he was anemic (Hgb 7.0 g/dL), and a positive stool guaiac test was noted. A computerized tomography scan with IV contrast showed a 5.5 cm large mass in the right colon with a severely narrowing colonic lumen. MRI reported a cecal mass and multiple subcentimeter mesenteric nodules suspicious for lymph node metastases or carcinomatosis. On colonoscopy, there was a 5.0 cm large, circumferential, fungating, and partially obstructing mass in the cecum (Figure 1A). Right hemicolectomy and omentectomy were performed to remove the cecal mass and regional lymph nodes. The tumor was pathologically staged as mucinous adenocarcinoma, pT3N0Mx (Figure 1B).
FIGURE 1: Cecal mass on endoscopy and microscopy

Endoscopy shows a 5.0 cm circumferential and partially obstructing mass in the cecum (A). Microscopic examination confirmed the diagnosis of stage pT3N0Mx mucinous adenocarcinoma (B, 200x).

In addition to the adenocarcinoma in the cecum, the mesentery is focally thickened with small nodular lesions. Histology shows sheets of large round or polygonal cells with abundant pale finely granular cytoplasm, distinct cytoplasmic border, round or ovoid nuclei with prominent nuclear membrane, vesicular chromatin, single or multiple conspicuous nucleoli, and frequent binucleation in some cells. Rare mitosis is present. Prominent histiocytes with raisinoid nuclei are also present among the aforementioned large cells, and infiltrating lymphocytes are seen in focal fibrous septa. Immunostains show the predominant large cells are mesothelial cells (strongly positive for calretinin and D2-40) mixed with histiocytes (strongly positive for CD68) (Figure 2). Immunostains for CD1a, S-100, and CD34 are negative (not shown). Findings are consistent with the diagnosis of mesenteric NHMH.

FIGURE 2: Morphologic features of mesenteric nodular histiocytic mesothelial hyperplasia (NHMH) on representative section

The mesenteric nodular lesions show predominantly histiocytes (inset: arrows) and mesothelial cells (inset: arrowheads) as well as lymphocytes within the delicate fibrous septa by H&E stains (A). Immunostains confirm the presence of mesothelial cells with positive calretinin (B) and D2-40 (C), as well as histiocytes with strongly positive CD68 (D).

Note: A 100x, B-D 600x

Discussion

In 1975, Rosai J and Dehner LP first described 13 cases of peculiar benign mesothelial hyperplastic lesions occurring during herniorrhaphy that closely resembled neoplastic processes, and they named this lesion ‘nodular mesothelial hyperplasia’ based on morphologic features in absence of immunohistochemical study.
With the help of immunohistochemical analyses, it was later found that such lesions were composed primarily of histiocytes, and the entity was subsequently re-named "nodular histiocytic/mesothelial hyperplasia (NHMH)" by Chan JK in 1997 [5]. NHMH has since been found, most often incidentally, in various anatomical sites throughout the peritoneum and beyond, causing unnecessary anxiety and ancillary studies as well as exploratory surgical procedures.

To our knowledge, our case is the first case of NHMH found in the mesentery related to colon adenocarcinoma; however, there are many other medical conditions associated with NHMH (Table 1). Histologically, 72 out of 74 (72/74) cases reported in literature showed histiocyte predomination (Table 1). Consistent with this finding, Ordonez NG recommended using ‘nodular histiocytic hyperplasia (NHH)’ to reflect the predominant cellular component of histiocytes in these lesions in 1998, instead of the terminology of NHMH [11]. One case reported by Bejarano PA showed a similar number of histiocytes and mesothelial cells [12], in contrast, our case exhibits a mesothelial cell predominance instead of histiocytes. Michal M compared the histologic features and immunoprofiles of 26 cases of NHMH, four cases of reactive eosinophilic pleuritis (REP), seven cases of mesothelial/monocytic incidental cardiac ex crescences (MICE), four cases of histioeosinophilic granuloma (HEG), and nine cases of intralymphatic histiocytosis (ILH), concluding that these five lesions are variants of the same entity under a process of reactive histiocytic hyperplasia. Given the histiocytes in all these lesions exhibited typical cytologic features, raisinoid or reniform nuclei, and a moderate amount of finely granular pale or eosinophilic cytoplasm, the authors proposed a new comprehensive term ‘histiocytosis with raisinoid nuclei’ [7]. Based on our experience, we believe the terminology of NHMH is more accurate since it includes both histiocytic and mesothelial cell populations, particularly for cases that are predominantly mesothelial cells such as our case.

| Ref | Age | Sex | Clinical history | Site | Gross | Microscopy |
|-----|-----|-----|------------------|------|-------|------------|
| [5] | 57  | m   | Rickettsial pneumonia | Lung | Transbronchial biopsy | Histiocyte-predominant |
| [8] | 71  | m   | Relapsed Inguinal hernia | Two nodules, 2.1 mm, 2.25 mm | Two nodules, 2.1 mm, 2.25 mm | Histiocyte-predominant |
| [2] | 36  | f   | Abortion | Pelvis | Solitary, fine, filmy adhesion band on the ovary | Histiocyte-predominant |
| [2] | 37  | f   | Abortions, endometriosis | Pelvis | 0.5 cm endometriotic implants, a solitary, firm filmy adhesion on ovary and fallopian tube | Histiocyte-predominant |
| [2] | elderly | m | Lung carcinoma | Lung | Transbronchial biopsy | Histiocyte-predominant |
| [2] | 53  | f   | Smoker, lung adenocarcinoma and carcinoi d | Lung | Transbronchial biopsy followed by wedge resections | Histiocyte-predominant |
| [2] | 47  | f   | Seasonal allergy, pericardial cyst | Pericardium | 6.0 cm lesion in the right cardiophrenic angle | Histiocyte-predominant |
| [4] | 46  | m   | Heart transplant, bilateral lung infiltrates | Lung | Transbronchial biopsy | A similar number of histiocytes and mesothelial cells |
| [16] | 25  | f   | Rheumatic pericarditis | Pericardium | 1.2 cm free-floating vegetation | Histiocyte-predominant |
| [3] | 60  | m   | Coronary artery disease | Pericardium | 1.5 cm cyst with nodules | Histiocyte-predominant |
| [4] | 1.5 | m   | Spermatocele | Left groin | Solitary cyst with 0.5 cm mural nodule | Histiocyte-predominant |
| [4] | 4.0 | m   | Spermatocele | Right paratesticular mass | 3 mural nodules, 0.1-0.3 cm | Histiocyte-predominant |
Mechanistically, there are two hypotheses to explain the formation of these lesions. One is reactive hyperplasia. It has been postulated that NHMH occurs as a non-specific localized reaction to irritations such as trauma, tumor, or inflammation that leads to the aggregation of histiocytes and interaction with mesothelial cells [5,7-8,13-14], which is consistent with our case of colon adenocarcinoma. The "artifact theory" was proposed as a counterpoint to the aforementioned hypothesis and describes a mechanism by which the mesothelial and histiocytic cells were seeded either during a prior procedure or during biopsy [13,15]. To date, there is insufficient evidence to exclude either, and thus, both theories may co-exist until we gain further understanding of these lesions. In this regard, future molecular studies on involved histiocytes and mesothelial cells might be helpful to better elucidate the nature of NHMH and the relationship among the aforementioned lesions in different locations.

**Conclusions**
NHMH is a rare entity that is most commonly encountered as an incidental finding. The main clinical significance of NHMH is its differential diagnosis with primary or metastatic diseases. It is important to be aware of its existence at different sites and histologic variations. An ancillary study to confirm biphasic cellular components of histiocytes and mesothelial cells may be necessary for challenging cases such as staging biopsies.

**Additional Information**

**Disclosures**

**Human subjects:** Consent was obtained or waived by all participants in this study. Loyola University Chicago Health Science Division Institutional Review Board (IRB) issued approval LU# 215401. The Loyola University IRB issued approval LU# 215401 for this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that there is no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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