Peritoneal or mesenteric tumours revealing histiocytosis

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ABSTRACT

Objective Peritoneal or mesenteric tumours may correspond to several tumour types or tumour-like conditions, some of them being represented by histiocytosis. This rare condition often poses diagnostic difficulties that can lead to important time delay in targeted therapies. Our aim was to describe main features of histiocytoses with mesenteric localisation that can improve the diagnostic process.

Design We performed a retrospective study on 22 patients, whose peritoneal/mesenteric biopsies were infiltrated by histiocytes.

Results Abdominal pain was the revealing symptom in 10 cases, and 19 patients underwent surgical biopsies. The diagnosis of histiocytosis was proposed by initial pathologists in 41% of patients. The other initial diagnoses were inflammation (n=7), sclerosing mesenteritis (n=4) and liposarcoma (n=1). The CD163/CD68+CD1a-histiocytes infiltrated subserosa and/or deeper adipose tissues in 16 and 14 cases, respectively. A BRAFV600E mutation was detected within the biopsies in 11 cases, and two others were MAP2K1 mutated. The final diagnosis was histiocytosis in 18 patients, 15 of whom had Erdheim-Chester disease. The median diagnostic delay of histiocytosis was 9 months. Patients treated with BRAF or MEK inhibitors showed a partial response or a stable disease. One patient died soon after surgery, and five died by the progression of the disease.

Conclusion Diagnosis of masses arising in the mesentery should be carefully explored as one of the possibilities in histiocytosis. This diagnosis is frequently missed on mesenteric biopsies. Molecular biology for detecting the mutations in BRAF or in genes of the MAP kinase pathway is a critical diagnostic tool.

INTRODUCTION AND OBJECTIVES

Peritoneal or mesenteric tumours detected by imaging may correspond to carcinomatosis or sarcomatosis of a previously unsuspected tumour, or to a primitive mesothelioma. It may also reveal atypical proliferations such as abdominal desmoid tumour, inflammatory pseudotumour, infections such as tuberculosis or be a manifestation of a systemic auto-immune or inflammatory disease, such as amyloidosis, Castleman disease or IgG4-related disease. Some of such rare conditions have been described as mesenteric panniculitis, mesenteric lipodystrophy or rectractile mesenteritis before being gathered into a single entity: sclerosing mesenteritis. A few cases of histiocytosis associated with peritoneal/mesenteric tumours have been reported.

CT scans or MRI are good imaging modalities for the detection of peritoneal/
Table 1  Clinical characteristics of the patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)/Sex</th>
<th>Revelatory symptom</th>
<th>Peritoneal involvement (mass/diffuse)</th>
<th>Surgical/Needle biopsy</th>
<th>First proposed histological diagnosis</th>
<th>Mutational status</th>
<th>Final diagnosis</th>
<th>Time delay until final diagnosis (months)*</th>
<th>Other organs involved</th>
<th>Evolution, status (months after biopsy)</th>
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<tbody>
<tr>
<td>01</td>
<td>73/M</td>
<td>Abd pain</td>
<td>Diffuse</td>
<td>Needle</td>
<td>Inflammation</td>
<td>WT*</td>
<td>ECD</td>
<td>7</td>
<td>Bones, r&amp;p,</td>
<td>AWD (21)</td>
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<tr>
<td>02</td>
<td>17/M</td>
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<td>Diffuse</td>
<td>Surgical</td>
<td>ECD</td>
<td>MAP2K1</td>
<td>ECD</td>
<td>51</td>
<td>r&amp;p, heart, kidney, testis</td>
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<td>Mass (3 cm)</td>
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<td>Mass</td>
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<td>ECD</td>
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<td>ECD</td>
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<td>DOD</td>
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<td>ECD</td>
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<td>ECD</td>
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<td>BRAF</td>
<td>ECD</td>
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<td>Liposarcoma</td>
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<td>Histiocytosis NOS</td>
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<td>Surgical</td>
<td>Inflammation</td>
<td>BRAF</td>
<td>ECD</td>
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<td>Bones, bone marrow</td>
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<td>Weight loss</td>
<td>Diffuse</td>
<td>Surgical</td>
<td>Inflammation</td>
<td>BRAF</td>
<td>ECD</td>
<td>2</td>
<td>Bones, r&amp;p, CNS</td>
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<td>Surgical</td>
<td>Inflammation</td>
<td>BRAF</td>
<td>ECD</td>
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<td>Needle</td>
<td>Sclerosing mesenteritis</td>
<td>WT*</td>
<td>Sclerosing mesenterits</td>
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<td>AWD (2)</td>
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<td>Surgical</td>
<td>ECD</td>
<td>MAP2K1</td>
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<td>Diffuse</td>
<td>Surgical</td>
<td>ECD</td>
<td>BRAF</td>
<td>ECD</td>
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<td>51/F</td>
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<td>Diffuse</td>
<td>Surgical</td>
<td>Inflammation</td>
<td>WT</td>
<td>Xanthogranulomatous peritonitis</td>
<td>17</td>
<td>No</td>
<td>AWD (2)</td>
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</table>

*Continued*
Table 1

<table>
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<tr>
<th>Case no.</th>
<th>Age (years)/Sex</th>
<th>Revelatory symptom</th>
<th>Peritoneal involvement (mass/diffuse)</th>
<th>Surgical/Needle biopsy</th>
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<th>Other organs involved</th>
<th>Evolution, status (months after biopsy)</th>
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</thead>
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<tr>
<td>21</td>
<td>66/M</td>
<td>Xanthelasma, retroperitoneal fibrosis</td>
<td>Diffuse</td>
<td>Surgical</td>
<td>Inflammation</td>
<td>BRAF</td>
<td>ECD</td>
<td>23</td>
<td>Liver, bones, r&amp;pr, pericardium, skin</td>
<td>AWD</td>
</tr>
<tr>
<td>22</td>
<td>54/M</td>
<td>General state alteration</td>
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<td>ECD</td>
<td>BRAF</td>
<td>ECD</td>
<td>6</td>
<td>Liver, bones, r&amp;pr, pericardium</td>
<td>AWD (9)</td>
</tr>
</tbody>
</table>

Patients 2 and 7 have mixed histiocytoses (ECD/RDD and ECD/Langerhans cell histiocytosis, respectively). Patient 11 had an associated chronic myelomonocytic leukaemia, patient 14 had an associated MDS and patient 7 developed a MDS during follow-up.

*Time between the first symptom (or, where we do not have the information, the date of the first peritoneal biopsy) and the diagnosis of histiocytosis.
†Molecular analysis limited to BRAFV600E, because of the low amount/quality of DNA obtained from the involved tissue.
‡Hepatomegaly.
Abd, abdominal; AWD, alive with disease; CNS, central nervous system; DOD, deceased of disease; ECD, Erdheim-Chester disease; F, female; M, male; MDS, myelodysplastic syndrome; NOS, not otherwise specified; RDD, Rosai-Dorfman disease; r&pr, retroperitoneal and perirenal; WT, no mutation of the genes of the MAP kinase pathway detected.

Figure 1

Initial and final diagnoses of patients within this cohort. Diagnosis of histiocytosis was proposed in 9/22 patients in initial pathology reports, and in 17 patients after central review.
follow-up information were obtained from patients’ medical records by electronic means. All patients (except #6 who died 2 days after surgery) had a clinical and imaging workup including 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan. All medical charts were centrally reviewed by two experimented clinicians (FC-A and JH) for retrieving the final diagnosis. For Erdheim-Chester disease (ECD) and other type of histiocytosis referred in Ambroise-Paré pathology centre during the period of study. These 1499 samples correspond to other organs such as bone (27%), skin (24%), perirenal (12%), lung (4.2%), etc.

The median age at the time of biopsy was 59 years, and female/male ratio was 6/16. Ten patients (45%) had abdominal pain as revelatory symptom (table 1). Three patients (14%) underwent a percutaneous biopsy, while all others underwent surgery. The diagnosis proposed in the initial pathology report did not include histiocytosis in 13 (59%) cases (figure 1A). Six patients (28%) had a unique peritoneal infiltration, while clinical and radiological investigations revealed other organ involvement in the 17 remaining cases (table 1). Imaging revealed (figure 2) that the lesions presented either as a mesenteric mass (n=11) or as multinodular/diffuse peritoneal infiltration (n=11).

All samples were infiltrated by mononucleated histiocytes, which had a foamy cytoplasm in the majority (18/22, 82%) of cases (table 2). Histiocytes with eosinophilic cytoplasm were also present in 13 cases (figure 3). The infiltration was superficial (ie, close to the serosa) in most (16/20, 80%) cases and deep (ie, infiltrating the adipose tissue of the omentum or the mesentery) in 14/20 (70%) cases (figure 3). In all cases, the phenotype was positive for CD163 (9/11) and/or CD68 and negative for CD1a. Only 4/20 (20%) cases were S100 positive.

A BRAFV600E mutation was detected in 11 (50%) patients, whereas 2 had a MAP2K1 gain-of-function mutation (p.(Gln56Pro) and p.(Lys57Asn)). Six of these mutated

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**RESULTS**

Twenty-three peritoneal or mesenteric biopsies, corresponding to 23 patients, were retrieved. Among them, one case was excluded because of the lack of tumour block and of clinical data. The 22 remaining cases corresponded to 1.5% of 1499 samples with the diagnosis or suspicion of histiocytosis referred in Ambroise-Paré pathology centre during the period of study. These 1499 samples correspond to other organs such as bone (27%), skin (24%), perirenal (12%), lung (4.2%), etc.

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A BRAFV600E mutation was detected in 11 (50%) patients, whereas 2 had a MAP2K1 gain-of-function mutation (p.(Gln56Pro) and p.(Lys57Asn)). Six of these mutated
cases expressed phosphoERK (figure 2), corresponding to an activation of the RAS-ERK pathway, and one was negative. For three patients, an extensive molecular analysis did not reveal any mutation within the MAP kinase pathway, one of whom was positive for phosphoERK. For the six other patients, real-time PCR did not reveal a mutation in the codon V600 of BRAF, but the amount and/or quality of available DNA were too low for further analyses using more sensitive methods on V600, or targeting other loci of BRAF and other genes of the MAP kinase pathway. Three of these latter patients expressed

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Fibrosis</th>
<th>Distribution of macrophages</th>
<th>Density of histiocytes</th>
<th>Cytoplasm of macrophages</th>
<th>Nuclei of macrophages</th>
<th>Giant cells</th>
<th>Phenotype</th>
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<td>1</td>
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<td>Low</td>
<td>Foamy</td>
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<td>S100, CD163+, CD1a+, pERK+</td>
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<td>Low</td>
<td>Eosinophil</td>
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<td>S100, CD163+, CD68+, CD1a+, pERK+</td>
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<td>S100, CD163+, CD68+, CD1a+, pERK+</td>
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<td>CD163+, CD68+, CD1a+, pERK+</td>
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<td>Yes</td>
<td>S100, CD163+, CD68+, CD1a+, pERK+</td>
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</table>

*Cytosteatonecrosis associated.
NA, not analysable.
phosphoERK, demonstrating a strong activation of this cell signalling pathway.

The final diagnosis of the disease was ECD in 15 patients, and histiocytosis not otherwise specified (NOS) for 2 additional patients (figure 1B). For patient #13, with final diagnosis of histiocytosis NOS, malignant histiocytosis could not be established on histology, because of low mitotic activity and low Ki67 index; however, this patient was resistant to treatments and finally deceased from disease progression. The median delay between the biopsy and the final diagnosis of histiocytosis was 9 months (range 2–49 months). The median age and disease extension were similar to those described in the largest series of patients with ECD.16

Single cases of histiocytosis with predominant peritoneal or mesenteric involvement have already been reported. Most of them corresponded to ECD and some to RDD.2-10 17 Rare cases of reactive histiocytosis have also been reported, such as crystal storing histiocytosis and nodular histiocytic aggregate of the omentum.18–20  As for our patients, in most of these cases the diagnosis of histiocytosis was not initially suspected. Our large series allows to define the main characteristics of these abdominal histiocytic diseases.

Histiocytes were either foamy or with eosinophilic cytoplasm, sometimes associated with Touton cells. The density of histiocytes (low, moderate or high) showed no correlation with symptoms claimed by the patients. Despite the low number of needle biopsies, we suspect that they can lead to diagnosis in abdominal masses, but surgery should be proposed in cases with diffuse peritoneal infiltration. Molecular analysis revealed BRAF or MAP2K1 mutations in 59% of patients, and was helpful to confirm diagnosis in most cases. These gain-of-function mutations are responsible for a constitutive activation of the MAP kinase signalling pathway, and are present in the majority of patients with ECD.14–21

Analysing this series of patients according to initial diagnoses might be helpful to avoid future misdiagnoses and to shorten diagnostic workup of forthcoming patients. A first group of four patients (#4, #10, #11, #17) were initially diagnosed as sclerosing mesenteritis, two of whom (#10, #11) were finally diagnosed with ECD with typical involvement of long bones, retroperitoneum, skin and/or orbits. The two other patients (#04, #17) were finally confirmed as sclerosing mesenteritis, since no other organ involvement was present and no mutation was detected. Sclerosing mesenteritis (or mesenteric panniculitis, mesenteric lipodystrophy or retraction mesenteritis) is a rare condition that presents symptoms...
associated with an abdominal mass. Up to 5.7% of cases are associated with autoimmune conditions such as hyper-IgG4 syndrome or lupus. Half of the patients do not require specific treatment.22 23 In a recently proposed flow diagram of initial workup for sclerosing panniculitis, a PET scan was recommended only for patients with lymph nodes >10 mm, in order to exclude lymphomas.24 Alexiou et al reported a woman aged 56 years diagnosed with a sclerosing mesenteritis 8 years before, who presented with ECD and died a few weeks later from central nervous system involvement.3 Similarly, Moore et al described another patient with sclerosing mesenteritis, who presented 1 year postsurgery with exophthalmos; a full skeletal assessment was performed which revealed ECD.2 Our data and the previously published cases suggest that full body FDG-PET scan should be proposed to all patients with suspected sclerosing mesenteritis, especially when blood examination shows abnormalities suggestive for myeloproliferative neoplasms.

A second group of seven other patients were diagnosed as inflammation of the peritoneum (#1, #6, #14, #15, #16, #20, #21). Five of them happened to have ECD (#1, #14, #15, #16, #21), and another one had histiocytosis NOS (#06). Patient #16 underwent 16 successive frozen sections during laparotomy, since a peritoneal carcinomatosis was suspected but could not be confirmed. Finally, a third group of nine other patients were suspected with ECD since the beginning (#2, #3, #5, #7, #8, #12, #18, #19, #22), and samples were sent to Ambroise-Paré Pathology Department for confirmation and/or for molecular analyses. Two out of these nine patients (#3, #5) were finally classified as sclerosing mesenteritis, confirming the difficult differential diagnosis between ECD and sclerosing mesenteritis, in the absence of extra-abdominal involvement and of a mutation activating the MAP kinase pathway. The major differences between diagnoses initially suspected and finally achieved, and the long delay to obtain this diagnosis, urged us to propose some recommendations for diagnostic process (figure 4).

The present paper has some limitations. It is a retrospective series and all samples were referred to our centre because of the suspicion of histiocytosis. Therefore, the proportion of sclerosing panniculitis which finally happened to be ECD is obviously overestimated. Similarly, a diffuse infiltration within the peritoneum by histiocytes may be related to several other aetiologies, including infections or tumours, and such cases were not referred to the French Histiocytosis Network.20 25 By contrast, the proportion of ECD patients with peritoneal or mesenteric involvement (1.53% of samples referred for suspicion of histiocytosis to the Ambroise-Paré Pathology Department) is obviously underestimated. Indeed, ECD usually involves other organs which are more accessible to fine needle biopsy. In a prospective study of 61 patients with extensive and standardised evaluation of disease extension, four (6.6%) patients had an infiltration of the mesentery, of whom one was diagnosed on a mesenteric biopsy.26 However, a diffuse infiltration of the peritoneum with nodules <5 mm may be undetectable with CT scan. The strength of our study is mainly based on a high number of cases contrasting with the published single case reports. Furthermore, all cases underwent phenotypic and molecular analyses. This allows us to draw conclusions based on different patterns that we observed. Several treatments have been used for patients with ECD and sclerosing mesenteritis (online supplemental table 1). In the present series, targeted therapies of ECD with either BRAF or MEK inhibitors induced partial responses in the majority of patients.
CONCLUSION
This large retrospective series shows that abdominal pain and peritoneal or mesenteric tumours may reveal or be associated with histiocytosis. We emphasise the fact that histiocytosis is a rare diagnosis to be made, but in those cases where the most common diagnoses for a mesenteric mass have been excluded, histiocytosis is a possibility to take into consideration. We suggest that a PET scan may ease this process of diagnosis by revealing secondary localisation of histiocytosis. The majority of our patients were initially misdiagnosed and there was an important time delay. Molecular analysis is a major diagnostic tool to confirm the diagnosis. Once the diagnosis of ECD is achieved, targeted therapies may be highly efficient even in those cases with peritoneal localisation.

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Contributors FC-A prepared the original manuscript draft and was in charge with the clinical analysis of the cases. IU prepared the original manuscript draft and was in charge with the histopathological analysis of the cases. JR handled clinical data collection and data analysis. FC was in charge with histopathology analysis. SV-D handled data collection and data analysis. ZH-R handled the interpretation of molecular tests. DC-H handled histopathological data collection and analysis. PD handled histopathological data collection and analysis. MO-C handled histopathological data collection and analysis. JS handled histopathological data collection and analysis. PT handled histopathological data collection and analysis. SH handled clinical data collection and data analysis. AM handled data collection and data analysis related to radiology. MK provided clinical data. LV handled histopathological data collection and analysis. CP handled clinical data collection and data analysis. AS handled clinical data collection and data analysis. AT handled data collection and data analysis. JD handled data collection and data analysis. OL handled data collection and data analysis related to radiology. JH designed and conducted the study, prepared the original manuscript draft and was in charge with the clinical analysis of the cases. J-Fe designed and conducted the study, prepared the original manuscript draft and was in charge with the pathology and molecular analysis of the cases. All the authors corrected and approved the final version of the manuscript.

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