CASE REPORT

ALK-positive anaplastic large cell lymphoma with a monomorphic small-cell pattern masquerading as inflammatory gastric lesions

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Abstract

Introduction: Anaplastic lymphoma kinase-positive (ALK+) anaplastic large cell lymphoma (ALCL) with a non-common pattern can be diagnostic challenging. Pathologists can be unavoidably and unintentionally blind to non-descript tumor cells in a lymphohistiocytic- (LH) or small-cell (SC)-pattern. We report a case of primary systemic ALK+ ALCL with a SC pattern that presented as secondary gastric lesions with a mixed LH and SC pattern that was masqueraded as inflammatory lesions. Case Report: A 34-year-old woman with intractable epigastric pain was referred to have repeated endoscopy with biopsy. She was found to multiple gastric erosions and nodules that were diagnosed as inflammatory lesions both endoscopically and histologically. Meanwhile, she developed an acute onset of severe back pain associated with a pathologic compression fracture in the T3 thoracic vertebral body. Imaging studies disclosed a disseminated systemic disease involving abdominopelvic lymph nodes and cervical and thoracic vertebral bodies. The needle biopsy of the pelvic lymph node disclosed diffuse proliferation of monomorphic small round cells that were diffusely positive for CD30 and ALK. A diagnosis of ALK+ ALCL with a monomorphic SC pattern was rendered. Discussion: A retrospective review of the gastric biopsies with the aid of immunohistochemistry enabled us to recognize the presence of lymphomatous infiltrates with a mixed LH and SC pattern in every piece of gastric biopsies that were repeatedly misdiagnosed as inflammatory lesions. This case illustrates a significant diagnostic pitfall of the LH- and SC-patterns in ALK+ ALCL, in which the tumour cells featuring lymphoid, plasmacytoid or histiocytoid appearance can be masqueraded as inflammatory cells.

Keywords: Anaplastic large cell lymphoma, anaplastic lymphoma kinase, monomorphic small-cell pattern, lymphohistiocytic pattern, stomach

INTRODUCTION

Systemic anaplastic lymphoma kinase-positive (ALK+) anaplastic large cell lymphoma (ALCL) can secondarily involve the gastrointestinal tract. The tumour involving the stomach usually appears histologically as a high-grade malignant tumour showing diffuse proliferation of large atypical lymphoid cells.1-3 The diagnosis of ALK+ ALCL with a common pattern is usually suggested by the morphology and confirmed by immunohistochemistry for ALK and CD30.4 However, the tumour can exhibit a wide spectrum of microscopic patterns depending on degree of atypia and pleomorphism of the lesional cell population and the abundance of bystander inflammatory cells such as lymphocytes, histiocytes, plasma cells, neutrophils, and eosinophils.5-9 ALK+ ALCLs with a lymphohistiocytic (LH) or small-cell (SC) pattern are particularly important because they can be misdiagnosed as inflammatory lesions as the tumour cells are difficult to recognise reliably based on histomorphology or cytomorphology alone without a high index of suspicion.7,8,10-13 In order to highlight a diagnostic pitfall of the LH- and SC-patterns in ALK+ ALCL, we report a case of ALK+ ALCL with a SC-pattern that initially presented as secondary gastric lesions with a mixed LH- and SC-pattern that was masqueraded as inflammatory lesions both endoscopically and microscopically.

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CASE REPORT

Clinical history
A 34-year old previously healthy woman presented to a local clinic with a two-week history of epigastric pain and odynophagia. The patient was found to have had an upper gastrointestinal endoscopy with multiple biopsies that showed dozens of discoid erythematous patches and nodules in the mucosa of the esophagus and stomach. The initial endoscopic biopsies of gastric and esophageal lesions were allegedly interpreted as severe acute and chronic inflammation. The symptoms were intractable to conservative treatment and she was referred to the hospital in order to have a repeated endoscopy with biopsy. She did not complain of any constitutional symptom. Her physical examination and past medical history were unremarkable. On the repeated endoscopy, she was found to have dozens of discrete erythematous patches, erosions (Fig. 1A) and nodules with or without a shallow central ulcer (Fig. 1B) in the antrum and body of the stomach. The largest nodules measured 0.5 to 1.5 cm in diameter. Multiple biopsies were taken for repeated histologic examination. As the diagnosis of gastric biopsies was reported as “inflammatory lesions”, the patient was treated conservatively for a week but with no response. Meanwhile, the patient was admitted due to a sudden onset of severe back pain. Imaging studies demonstrated the presence of multiple nodules in both lungs, significant abdominopelvic lymphadenopathies (Fig 2A) and a pathologic compression fracture in the T3 thoracic vertebral body (Fig. 3A). An ultrasound-guided needle biopsy of the left iliac lymph node was performed. Subsequently, the patient underwent an emergency decompression surgery for the T3 compression fracture.

Pathology
Biopsies from the gastric erosions showed expanded lamina propria due to mononuclear infiltrates along with infiltration of neutrophils and eosinophils. The mononuclear cells featured the appearance of lymphoplasmacytoid or lymphohistiocytoid cells (Fig. 1C, 1E, and 1G). Biopsies from nodular gastric lesions with a central shallow ulcer demonstrated dense mononuclear infiltrates along with abundant neutrophilic infiltration resulting cryptitis and crypt abscesses and regenerative and degenerative changes in surface and crypt epithelium (Fig. 1D, 1F, and 1H). Helicobacter pylori-like organism was not identified. All the biopsies were diagnosed as inflammatory lesions. Although there was no endarteritis or endophlebitis, a possibility of syphilitic gastritis was included in the differential diagnosis. However, Warthin-Starry stains were negative for spirochetes.

The needle biopsy of the pelvic lymph node revealed a diffuse lymphomatous infiltrate composed of monomorphic small to medium-sized lymphoid, some of which exhibited histiocytoid or plasmacytoid cytomorphology (Fig. 2B-2C). On immunohistochemistry, the tumour cells were negative for leukocyte common antigen (LCA, CD45), CD3, CD20, CD138, and PAX5 but positive for MUM1. EBV-encoded RNA was not detected by in situ hybridisation. However, immunohistochemistry for CD30 (Fig. 2D) and ALK (Fig. 2E) helped to achieve a correct diagnosis of ALK+ ALCL with a monomorphic SC-pattern. Histologic examination of the T3 vertebral body also showed the same lymphomatous infiltration consisting predominantly of small lymphoid cells (Fig. 3B-3C) that were diffusely and strongly positive for CD30 (Fig. 3D) and ALK (Fig. 3E).

Subsequently, the gastric biopsy slides were reviewed with a high index of suspicion kept mononuclear cells infiltrating within the lamina propria. Retrospectively, with the aid of immunohistochemistry for CD30 and ALK, we were able to identify in every single piece of the gastroscopic biopsy samples – all 6 pieces of them - conspicuous lymphomatous infiltrates consisting predominantly of atypical lymphoid cells with a plasmacytoid or histiocytoid appearance that could be misinterpreted at first as reactive lymphoid cells or histiocytes (Fig. 4). With the help of hindsight, we were also able to recognise more sparse individual tumour cells characterised by irregularly folded or indented nuclei resembling those of hallmark cells of ALCL (Fig. 5). Finally, the diagnosis of all the gastric lesions was revised as ALK+ ALCL with a mixed LH and SC pattern.

Laboratory findings and clinical outcome
Her initial lab tests were within the normal limits except for slightly elevated lactate dehydrogenase (217 IU/L; reference range, 106-211 IU/L) and beta-2 microglobulin (2.71mg/L; reference range, 1.00-2.40 mg/L). The serologic tests for syphilis and HIV were negative. Staging work-up with further imaging studies and bone marrow biopsy were followed.
FIG. 1: Gastric endoscopy discloses erythematous nodules without (A) or with surface erosion/ulceration (B). Endoscopic biopsy of the nodules shows abundant infiltration of histiocytoid and plasmacytoid mononuclear cells (C, ×100; E, ×200; G, ×400). Endoscopic biopsy of the nodule with erosion/ulceration shows an extensive infiltration of neutrophils forming crypt abscesses (D, ×100) and degenerative/reparative change of the foveolar epithelium (F, ×200) in addition to an extensive infiltration of histiocytoid/plasmacytoid mononuclear cells (H, ×400). All magnifications are original microscope magnification.
FIG. 2: Computed tomography scan reveals multiple lymphadenopathies in the abdominal and pelvic cavity (A). The needle biopsy of the left iliac lymph node demonstrates a diffuse lymphomatous infiltrate (B, ×100) composed of monomorphic small round cells with plasmacytoid or histiocytoid features (C, ×600) that are positive for CD30 (D, ×200) and ALK (E, ×200). All magnifications are original microscope magnification.

The bone marrow biopsy showed normocellular marrow with sparse CD30-and ALK-positive lymphoma cells that were not appreciated on the H&E stained sections. A PET-scan revealed widespread disease in the pelvic, abdominal, and mediastinal lymph nodes. The patient underwent 8 cycles of chemotherapy with the CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen followed by autologous peripheral blood stem cell transplantation (APST). However, the patient relapsed 1 year after APST and was lost to follow-up.

DISCUSSION

ALK+ ALCL is a well-defined distinctive group of CD30+ peripheral T-cell lymphomas that are
characterised by aberrant expression of ALK protein associated with genetic alterations involving the ALK gene. The heterogeneity of clinical and pathological features of ALK+ ALCL can present a diagnostic challenge to pathologists. The morphology of the tumour ranges from small-cell neoplasms mimicking inflammatory lesions to the opposite extremes with overtly malignant features. In addition to the common pattern (accounting for 60-70%).

FIG. 3: Computed tomography scan discloses a pathologic compression fracture in the T3 vertebral body (A, arrow). The bone is infiltrated and destroyed by the lymphomatous infiltrate (B, H&E, ×100; C, H&E, ×600) that are positive for CD30 (D, ×200) and ALK (E, ×200). All magnifications are original microscope magnification.
FIG. 4: Retrospective histologic review of the gastric erosions (A, H&E, ×40) and immunohistochemical studies for CD30 (B, ×200; inset, ×600) and ALK (C, ×200; inset, ×600) reveals the lymphomatous infiltration in the lamina propria, consisting predominantly of small but pleomorphic mononuclear cells (D, H&E, ×200) with histiocytoid (E, H&E, ×600) or plasmacytoid (F, H&E, ×600) cytomorphology. All magnifications are original microscope magnification.

a variety of non-common microscopic patterns have been described: lymphohistiocytic (LH) pattern accounting for 10%, small-cell (SC) pattern accounting for 10%, composite (or mixed) pattern accounting for 10 to 20%, and other rare patterns such as Hodgkin-like, clear cell, signet ring cell, and sarcomatoid pattern.\textsuperscript{14,15} Although microscopic patterns do not seem to be associated with prognostic or therapeutic significance, the recognition of LH- and SC-patterns is important because the tumours with these patterns can be misdiagnosed as reactive or inflammatory lesions.\textsuperscript{14,16,17} This is particularly true in small biopsy samples from extranodal sites such as endoscopic biopsies that are not large enough for a detailed histoarchitectural assessment.

ALK\textsuperscript{+} ALCL uncommonly involves the stomach primarily or secondarily.\textsuperscript{18} While primary
ALK-POSITIVE ALCL WITH SMALL CELL PATTERN

FIG. 5: Retrospective histologic review of the gastric nodules with a central ulcer (A, H&E, ×10.25; B, H&E, ×40; C, H&E, ×200) discloses extensive infiltration of the lamina propria with small but pleomorphic mononuclear cells with plasmacytoid appearances (D, H&E, ×600). The atypical mononuclear cells are negative for CD3 (E, ×100), CD20 (F, ×100), CD45 (G, ×100), CD2 (H, ×100), and CD5 (I, ×100). Immunostains for CD30 (J, ×100) and ALK (K, ×100) confirms the presence of a conspicuous lymphomatous infiltration through the lamina propria of the mucosa, which can be obscured by intervening inflammatory cells including abundant histiocytes (L, CD68, ×100). All magnifications are original microscope gastric lesions usually appear endoscopically as large mass-forming lesions that result in clinical symptoms\textsuperscript{13,19,20}, secondary gastric lesions tend to present endoscopically as multiple nodules with or without a central aphthoid ulcer (Table 1). Similarly to the previously reported secondary gastric lesions\textsuperscript{21}, the gastric lesions in our case also appeared endoscopically as erythematous patches, erosions and small nodules with or without a superficial ulcer. Microscopically, however, in contrast to classical ALK\textsuperscript{+} ALCL with a common pattern that appears overtly malignant with conspicuous diagnostic hallmark cells, the gastroscopic biopsies taken from the secondary gastric lesions in our case lacked overtly malignant histologic features. Because the predominant tumour cells in the gastric lesions were small to medium in size, with cytomorphologic features resembling reactive lymphoid cells or histiocytes, the gastric mucosal lesions in our case were wrongly interpreted at first as severe active inflammatory lesions.\textsuperscript{22}
# TABLE 1. Clinicopathologic features of secondary gastric involvement of ALK-positive anaplastic large cell lymphoma

<table>
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<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Clinical presentation</th>
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<tr>
<td>1</td>
<td>27/F</td>
<td>Cervical LAD (due to ALK+ ALCL) and anorexia</td>
<td>Multiple small ulcerations with a red halo (aphthoid ulcerations) throughout the stomach</td>
<td>Diffuse infiltration of atypical large lymphocytes</td>
<td>Common pattern</td>
<td>CD45+, CD30+, ALK+</td>
<td>Matsumoto et al.¹ (2005)</td>
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<td>2</td>
<td>23/F</td>
<td>Cervical LAD (due to ALK+ ALCL) and epigastric pain</td>
<td>Multiple aphthoid ulcerations</td>
<td>Diffuse infiltration of atypical large lymphocytes</td>
<td>Common pattern</td>
<td>CD45+, CD30+, ALK+</td>
<td>Matsumoto et al.¹ (2005)</td>
</tr>
<tr>
<td>3</td>
<td>21/F</td>
<td>Cervical LAD (due to ALK+ ALCL)</td>
<td>Submucosal tumors with a central ulcer</td>
<td>Diffuse and solid infiltration of pleomorphic large lymphoid cells with abundant cytoplasm</td>
<td>Common pattern</td>
<td>CD45+, CD30+, ALK+</td>
<td>Ishii et al.² (2011)</td>
</tr>
<tr>
<td>4</td>
<td>34/F</td>
<td>Intractable epigastric pain followed by sudden onset of a T3 compression fracture</td>
<td>Dozens of erythematous patches and nodules with or without a central ulcer</td>
<td>Marked lymphohistiocytic/lymphoplasmacytic and neutrophilic infiltration with conspicuous cryptitis and crypt abscesses</td>
<td>Mixed lymphohistiocytic and small-cell pattern</td>
<td>CD45, CD3⁺, CD20⁺, CD30⁺, ALK⁺</td>
<td>Present case</td>
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F, Female; LAD, lymphadenopathy; NA, not available; ALK, anaplastic lymphoma kinase; ALCL, anaplastic large cell lymphoma
The nodal and vertebral lesions in our case showed a monomorphic SC-pattern. This pattern was previously described in two cases presenting with splenic rupture. By contrast, the gastric lesions in our case showed a mixed LH- and SC-pattern characterised by heterogeneous cellular infiltrates that were overwhelmed by a predominant population of non-descript tumour cells with lymphohistiocytoid or lymphoplasmacytoid cytomorphology. The lesions were misdiagnosed at first as infectious gastritis because of the difficulties in the detection of malignant nature of lesional cells that were not much different morphologically from bystander inflammatory cells such as reactive lymphoid cells or histiocytes. Instead, the presence of focus with mixed inflammatory infiltrates and extensive cryptitis and crypt abscesses due to extensive neutrophilic infiltration mislead the original sign-out pathologist to consider a possibility of syphilitic gastritis in the differential diagnosis until further histochemical and serologic tests for syphilis sufficiently proved to be negative. Syphilitic gastritis can also be characterised endoscopically by multiple nodules and erosions and histologically by chronic active inflammation with dense lymphoplasmacytic infiltration along with mixed inflammatory infiltrates distorting the glandular architecture. Retrospectively, with the help of hindsight, however, we were able to recognise the presence of a clue in the differential diagnosis: the presence of sparsely scattered hallmark cells with an eccentrically located kidney-shaped or folded nucleus and an eosinophilic paranuclear hof. Finally, with aid of immunohistochemical stains for CD30 and ALK that demonstrated many small but pleomorphic neoplastic lymphocytes with atypical nuclei and more sparsely scattered hallmark cells, the diagnosis of all the gastric biopsies was revised as gastric involvement of ALK+ ALCL with a mixed LH- and SC pattern. Ponzoni et al. reported a similar case to ours, which presented as a brain lesion misdiagnosed at first as an inflammatory lesion.

The non-common patterns in ALK+ ALCL can be diagnostically challenging for general pathologists not only due to the lack of classical hallmark features but also due to an abundance of reactive bystander cells that obscure the tumour cells. The LH- and SC-patterns are particularly important in that general pathologists can be unavoidably and unintentionally blind to the presence of small but pleomorphic lymphoma cells with plasmacytoid or histiocytoid cytomorphology that are much smaller and sparser compared to those in the common pattern. Due to the lack of conspicuous cytologic atypia or marked cellular pleomorphism, the SC pattern in small biopsy samples from extranodal sites can also be misinterpreted as a reactive process. The presence of tumour cells in the LH-pattern involving extranodal sites can also be obscured by the abundant reactive histiocytes. Hence, the histologic distinction of ALK+ ALCL with these non-common patterns from histologic mimickers should essentially be based on a high index of suspicion kept for hallmark cell-like atypical mononuclear cells with an eccentric reniform nucleus and a prominent paranuclear Golgi region. Furthermore, because the tumour cells can also be negative for LCA, CD3, and CD20 as in our case, the correct diagnosis can only be substantiated by immunohistochemical studies using a panel of antibodies including those for CD30 and ALK.

In summary, in order to highlight the potential pitfalls in the diagnosis of ALCL with non-common patterns, we presented a case of primary systemic ALK+ ALCL with a monomorphic SC pattern presenting initially as gastric lesions with a mixed LH- and SC pattern that was masqueraded as inflammatory lesions. Pathologists should be aware of these rare patterns in ALK+ ALCL in which the hallmark cells are much smaller and sparser compared to those in ALK+ ALCL with a common pattern.

Conflict of interest: There is no potential conflict of interest relevant to this article.

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REFERENCES