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Case Study

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GASTRIC ANAPLASTIC LARGE CELL LYMPHOMA ALK POSITIVE REVEALED BY HEMATEMESIS

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ABSTRACT

Anaplastic large cell lymphoma (ALCL) is a rare hematological malignancy and a distinct subtype of mature T-cell lymphomas. ALCL includes two distinct entities: anaplastic lymphoma kinase (ALK) positive and ALK negative. The most common sites of ALCL involvement are lymph nodes, followed by skin, bone and soft tissue. Here, we report a rare case of a 31-year-old man with ALCL ALK positive infiltrating the stomach in addition to lymph nodes. Gastric involvement was revealed by hematemesis. The lymphoma was classified stage III. A complete tumor response after chemotherapy type CHOP was obtained.

KEYWORDS: anaplastic large cell lymphoma ALK positive, lymph nodes, stomach.

INTRODUCTION

Anaplastic large cell lymphoma (ALCL) was first identified by Stein et al. in 1985.[1] ALCL is a rare hematological malignancy and a distinct subtype of mature T-cell lymphomas.[2] According to the World Health Organisation (WHO) classification primary systemic ALCL includes two distinct entities: anaplastic lymphoma kinase (ALK) positive and ALK negative.[3] The most common sites of ALCL involvement are lymph nodes, followed by skin, bone and soft tissue. Gastrointestinal ALCL was rarely reported.[4] Here, we report a rare case of ALK-positive ALCL infiltrating the stomach in addition to lymph nodes with a complete tumor response after chemotherapy type CHOP.

CASE STUDY

A 31-year-old man presented with a 2-months history of abdominal pain without fever or transit problems. He reported a weight loss of 15 kg in 2 months. His past and family histories were unremarkable. On examination, he had mucocutaneous jaundice without hepatosplenomegaly or superficial lymphadenopathy. Laboratory examination showed abnormalities as follows: white blood cell counts: 10 300/mm3; hemoglobin:10.7 g/dL; C- reactive protein:105 mg/L,GGT:511UI/L (10ULN), ALP: 285UI/L(2ULN), BIL: 122/85, ALT: 47UI/L, AST:54 UI/L(1.5ULN). Computed tomography of the neck, chest, abdomen, and pelvis showed voluminous ganglionic flows hypodense partially necrotic coeliomenteric, in hepatic pedicle, latero and retro aortic. These ganglionic masses enclose the portal trunk and the main bile duct with dilatation of the intrahepatic bile ducts. A biopsy of a retroperitoneal lymph node was performed under scanning control. Microscopic examination showed diffuse and malignant tumor proliferation made of large atypical lymphoid cells with abundant cytoplasm and an eccentric kidney-shaped and horseshoe-shaped nuclei. Immunohistochemistry revealed that the neoplasic cells were positive for CD30, anaplastic lymphoma kinase (ALK) and epithelial membrane antigen (EMA). After 48 hours of hospitalization, the patient presented an hematemesis. Upper gastrointestinal endoscopy identified, on the gastric small curvature, two elevated lesions with central ulcer covered with hematin. Biopsies taken from these lesions showed the similar features than lymph node biopsies showing lymphoid large sized cells with pleomorphic nuclei (Fig. 1) and a high expression of CD30 (Fig. 2), ALK (Fig. 3) and EMA (Fig 4). EBV serology was negative. Bone marrow biopsy revealed no tumor cells infiltration. Thus, a definitive diagnosis of ALCL stage III, involving lymph nodes and the stomach was made. Combined chemotherapy type CHOP including Cyclophosphamide 500 mg/m2 , doxorubicin 50 mg/m², vincristine 1 mg/m² and Prednisone 40 mg/m² was entertained. After 8 courses of chemotherapy, morphologic and endoscopic control showed a disappearance of all anomalies.

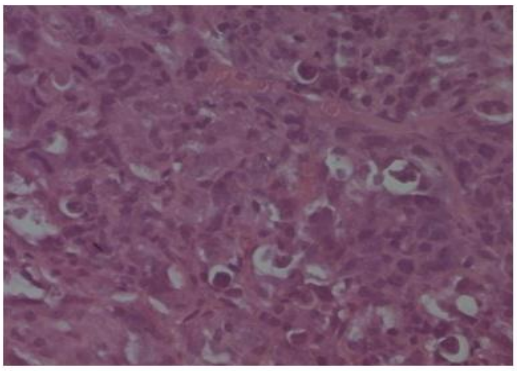

Figure 1: (x 400): lymphoid large sized cells with high pleomorphic nuclei and mitosis

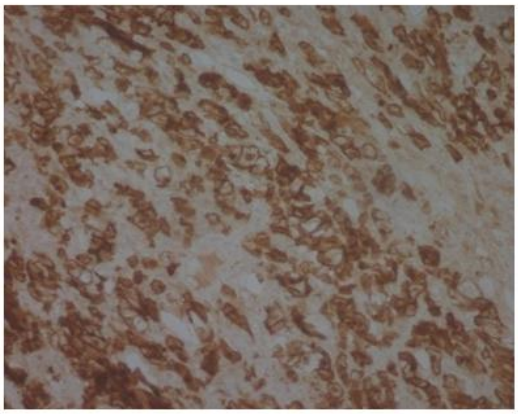

Figure 2: (x 400): tumoral cells expressing CD 30

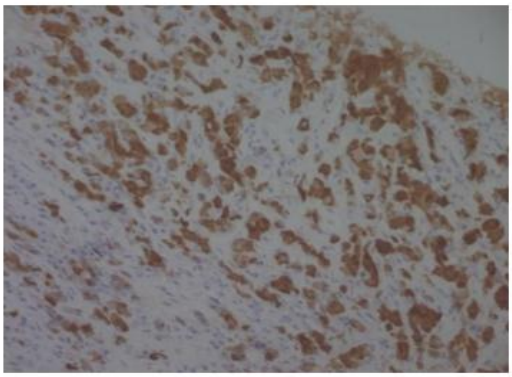

Figure 3: (x 400): tumoral cells expressing ALK (anaplastic lymphoma kinase)

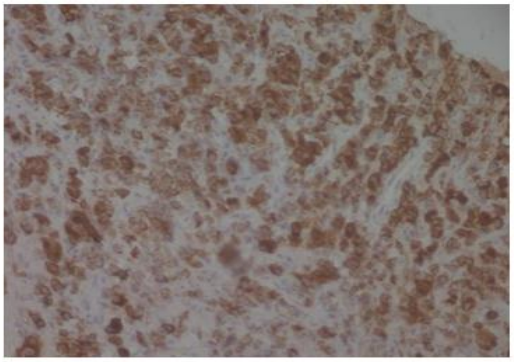

Figure 4: (x 400): tumoral cells expressing EMA (epithelial membrane antigen)

DISCUSSION

The rarity of anaplastic lymphoma and its infiltration of the gastric wall make the originality of this observation. Indeed, Stomach is the commonest site of extranodal lymphoma followed by small intestine. But, most of gastrointestinal lymphomas are non-Hodgkin lymphomas, with B-cell dominating over T-cell type, and mucosa-associated lymphoid tissue lymphoma is the most common subtype.[5] A few rare variants such as ALCL and follicular lymphoma are also observed.[2] Fewer than 100 cases have been reported, most of which are from Japan.[6,7] ALCL consists of a subgroup of non-Hodgkin's lymphoma (NHL). It is a peripheral T-cell lymphoma characterized with strong expression of CD30.[8] ALCL mostly affects lymph nodes, with uncommon involvement of extranodal sites, observed in 60% of cases, including soft tissue, bone, lung and liver.[9] Cases of ALCL involving the stomach are therefore very rare.

According to the expression of ALK, ALCL is divided into two categories: primary systemic ALK positive ALCL and primary systemic ALK negative ALCL. Our patient had ALCL ALK positive.

ALK+ ALCL accounts for about 3% of adult non-Hodgkin lymphomas (NHL) and 10–15% of childhood lymphomas.[10] ALK+ ALCL is an aggressive lymphoma that occurs in young subjects (median age: 34 years), with a male predominance (M:F ratio = 1.5).[11]

No particular risk factors have been clearly identified for ALCL. Presently, there is no convincing evidence that viruses causing NHL in humans, such as Epstein–Barr virus, are involved in the origin of ALCL. The pathogenetic implication of the t (2;5) chromosomal translocation and NPM (nucleophosmin)-ALK fusion product are matter of study.[10] In fact, approximately 90% of ALK+ ALCL show clonal rearrangement of the *TCR* genes. The most frequent genetic alteration is a translocation, t(2;5)(p23;q35), between the *ALK* gene on

chromosome 2 and the nucleophosmin (*NPM*) gene on chromosome 5.[12] Many other chromosomal rearrangements or gene mutations leading to enhanced ALK activity have subsequently been identified.[10] In our case, EBV serology was negative but the genetic study was not made.

Patients with ALK+ ALCL frequently present with advanced stage disease (stage III–IV 65% of cases) and systemic symptoms (75%), especially fever. Central nervous system localization is rare. Bone marrow involvement consists of infiltration as single neoplastic cells. This is identified in 11% of the cases when assessed by haematoxylin and eosin staining, and in 30% if immunohistochemistry is performed.[13] The clinical presentation of our patient was atypical with no fever but with a significant weight loss. Lymphoma was classified as stage III. Bone marrow biopsy revealed no tumor cells infiltration.

ALK positive ALCL is typically associated with large tumor cells that exhibit an abundant cytoplasm and pleomorphic nuclei, often horseshoe-shaped and elevated expression of ALK protein as well as of CD30 on the cell membrane and in the Golgi region.[14]

Unlike ALK negative ALCL, ALK-positive ALCLs are usually sensitive to a multidrug chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone).[2] There is no defined chemotherapy combination for ALCL and the majority of prospective trials have been performed in children. Based on retrospective series, doxorubicin-containing polychemotherapy, typically CHOP, is the standard first-line treatment for ALK+ ALCL, which is associated with an overall response rate of 90% with 60% of patients remaining relapse free at 5 years.[9,15] Our patient received chemotherapy type CHOP with a complete tumor response.

The prognosis of ALK+ ALCL is remarkably better than other T-cell lymphomas.[16] Overall survival (Os) of ALK+ ALCL is far better than ALK - ALCL, with 5-year OSs of 71% and 15%, respectively.[10]

CONCLUSION

ALK positive ALCL is a very rare type of lymphoma that affects young male subjects. Lymph node involvement is common. However, the extra-nodal involvement of the stomach is exceptional. Unlike other types of lymphoma, EBV infection is not incriminated in the lymphogenesis of ALCL. However, the role of genetic alterations such as the translocation t (2; 5) has been suggested. This type of lymphoma is often aggressive but once treated it responds well to chemotherapy with a good prognosis.

No conflicts of interest.

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