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Case study

Primary mucosa-associated lymphoid tissue lymphoma of the gallbladder: report of a case harboring *API2/MALT1* gene fusion ☆

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Summary The genetic alterations underlying extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue type are heterogeneous and show variation according to the tumor site. Here, we report a case of mucosa-associated lymphoid tissue lymphoma of the gallbladder with genetic characterization. This lymphoma, diagnosed in a 75-year-old woman who underwent cholecystectomy for suspected acute cholecystitis, presented as diffuse thickening of the gallbladder wall. The morphology was typical of mucosa-associated lymphoid tissue lymphoma, and by immunophenotype, the tumor cells were CD20+ CD5− CD10− CD23− CD43− BCL6− BCL2+ IgM+ IgD− λ+, with moderate nuclear expression of BCL10. Interphase fluorescence in situ hybridization analysis on paraffin sections, using a fusion probe for *API2*/*MALT1*, demonstrated 2 fusion signals in most nuclei, bringing the first documentation of a t(11;18)(q21;q21) in this exceptional primary disease location.

1. Introduction

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) accounts for 7% to 8% of all B-cell lymphomas and most commonly occurs in the gastrointestinal tract, especially in the stomach. Other common sites include the salivary glands, lungs, orbit

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and ocular adnexa, skin, thyroid, and breast. Multiple extranodal sites may be involved in up to 10% of the cases at the time of presentation [1]. Typically, MALT lymphomas arise in a lymphoid tissue that is acquired in the setting of chronic inflammation and prolonged lymphoid reactive proliferations, in response to either infectious conditions (eg, *Helicobacter pylori* gastritis) or autoimmune disorders (eg, Hashimoto thyroiditis or Sjögren syndrome). This disease has indeed been proposed as a model of how sustained inflammation increases the risk of genotoxic insults and oncogenesis [1].

Several chromosomal translocations, which appear to be specific for MALT lymphoma, occur at variable frequency according to the primary location of disease [2,3]. The t(11;18)(q21;q21), leading to the fusion of the apoptosis inhibitor-2 (*API2*) gene and the MALT lymphoma-associated translocation (*MALT1*) gene, is the most frequent (detected in 10% to 35% of the cases) and shows a marked predilection for gastrointestinal and pulmonary MALT lymphomas. The t(14;18)(q32;q21), resulting in rearrangement of the *MALT1* gene to the immunoglobulin heavy chain (*IGH*) locus, occurs in 3% to 11% of MALT lymphomas and is mainly detected at nongastrointestinal sites, such as ocular adnexa, salivary glands, skin, lung, and liver. The t(1;14)(p22;q32), described primarily in the gastrointestinal tract and the lung, is rare (<5% of the cases) and results in rearrangement of the B-cell lymphoma 10 (*BCL10*) gene to the *IGH* gene [1-4]. Remarkably, these 3 translocations seem to promote lymphoma development by a common mechanism, leading to the constitutive activation of the nuclear factor-κB signaling pathway [1].

Primary involvement of the gallbladder by MALT lymphoma is extremely rare. Of the few cases reported in the literature, none has been documented at the genetic level [5-13]. Here, we report a case of primary MALT lymphoma of the gallbladder with evidence of *API2*/*MALT1* gene fusion, indicative of a t(11;18)(q21;q21) translocation.

2. Case report

A 75-year-old woman with no significant medical history presented with a few days' history of right upper abdominal pain and fever. Physical examination revealed pronounced tenderness over the right hypochondrium. No lymphadenopathy was noted. Routine laboratory tests showed a normal white blood cell count but increased neutrophilia and an inflammatory syndrome. Abdominal ultrasonography demonstrated thickening of the gallbladder wall and several stones. *Escherichia coli* was detected in blood cultures. Antimicrobial therapy was administered, and laparoscopic cholecystectomy was performed on the next day after the admission.

The resected gallbladder, received open, measured 6.5 cm in length and 3 cm in diameter and contained no visible gallstones. Grossly (Fig. 1A), the bottom and the distal portion of the wall were circumferentially thickened (up to 1 cm) and firm over more than 4 cm. The overlying mucosa had a trabeculated and granular appearance, and the serosa was congestive. The cystic duct had a normal diameter and contained no stone. No cystic lymph node was identified.

Histologic examination (Fig. 1B-E) revealed a diffuse and vaguely nodular dense lymphoid infiltrate, extending from the mucosa down to the serosa and surrounding reactive lymphoid follicles. Mucosal folds were preserved although widened and shortened. The infiltrate comprised mainly small monotonous-looking lymphoid cells, harboring slightly irregular nuclei with mottled chromatin and surrounded by a moderately abundant clear cytoplasm. Scattered blasts were identified. There was no obvious plasmacytic differentiation. Some of the rarefied epithelial crypts exhibited lymphoepithelial lesions. The gallbladder wall adjacent to the tumor showed features of slight chronic cholecystitis. Special stains failed to reveal any microorganism. The resection margin at the cystic canal was free of lymphomatous infiltration.

By immunohistochemistry (Fig. 2A-F), the lymphoid infiltrate was diffusely positive for CD20, with monotypic IgM λ staining. The lymphoma cells were negative for IgD, CD5, CD43, CD10, and BCL6, and positive for BCL2. CD21 immunostaining disclosed remnants of follicular dendritic cell networks, associated with reactive follicles. Ki-67 was expressed in less than 5% of lymphoid cells outside the germinal centers. The presence of lymphoepithelial lesions in the epithelium was highlighted by cytokeratin staining. Some small dispersed T lymphocytes were positive for CD3, CD5, and CD43. Immunostaining for BCL10 produced a moderate nuclear staining in most lymphoma cells.

Interphase fluorescence in situ hybridization (FISH) analysis performed on paraffin sections with *MALT1* split signal DNA probe (Dako, Glostrup, Denmark) demonstrated 39% of isolated signals, consistent with *MALT1* gene rearrangement (cutoff, 10%). *IGH*/*MALT1* fusion probe (Fig. 2G) confirmed *MALT1* gene rearrangement, showing 3 isolated orange signals in more than 50% of nuclei examined; however, *IGH* gene was not rearranged (2 green signals per nucleus), and there was no evidence of *IGH*/*MALT1* fusion signals. Finally, a t(11;18)(q21;q21) translocation was demonstrated with the *API2*/*MALT1* fusion probe (Fig. 2H), which showed 2 fusion signals in more than 50% of the nuclei.

The staging procedure comprised upper and lower digestive tract endoscopy with biopsies (from gastric corpus, gastric antrum, duodenum, ileum, and colon), upper airways examination, chest and abdomen computed tomography scans, positron emission tomography scan, and bone marrow biopsy. A small focus of lymphoid infiltrate was found in the duodenal mucosa, composed of CD20-positive small B cells, with nuclear positivity for BCL10 and λ light chain restriction. A seminested polymerase chain reaction–based assay [14] showed the same monoclonal rearrangement of the *IGH* locus in the gallbladder