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Case Report
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Diffuse Large B cell Lymphoma Presenting as Acute Pancreatitis: Case Report and Literature Review

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Abstract

Background: Acute pancreatitis as an initial symptom of Diffuse Large B Cell Lymphoma (DLBCL) is rarely reported. The relationships between DLBCL and Pancreatitis seldom been discussed before. A case of a 58-year-old male man presenting with severe abdominal pain and elevated pancreatic enzyme, who diagnosed as acute pancreatitis first but DLBCL later after pathological biopsy, was reported in this paper.

Methods: General laboratory examinations, whole body PET-CT, thyroid tumor biopsy and immunohistochemistry, bone marrow examination, cytogenetic analysis, and PCR were performed.

Results: After standard treatment of pancreatitis and R-CHOP regiment chemotherapy, his abdominal pain relieved and extranodal tumors greatly reduced.

Conclusion: The possibility of DLBCL should be reminded when distinguishing a patient presenting as acute pancreatitis with no obvious cause or poor therapeutic effect despite standard therapy.

Keywords: Acute pancreatitis; Diffuse large B cell lymphoma; Thyroid tumor

Case Presentation

A 58-year-old male patient was urgently sent to our hospital for vomiting and severe epigastrium pain radiating to back on August 13th, 2021. A physical examination on admission revealed that there were tenderness and rebound pain on his epigastrium, with neither abdominal mass nor hepatosplenomegaly, but unexpectedly found multiple thyroid solid tumors and cervical enlarged lymph node. There was no history exposure to drugs, tuberculosis and alcohol consumption. His neither personal nor family history was out of particularity.

His blood biochemistry showed obviously elevated serum amylase 532 U/L (normal range, 0 U/L to 125 U/L), serum lipase 739 U/L (normal range, 13 U/L to 60 U/L), hypersensitive C-Reactive Protein (hsCRP: 13.30 mg/L; normal range, 0 mg/L to 3 mg/L). White Blood Cell (WBC) count was 10.57×10^9 cells/L (3.5×10^9 to 9.5×10^9), Hemoglobin (Hb) was 125 g/L (130 g/L to 175 g/L), Platelet (Plt) 297×10^9 cells/L (100×10^9 to 350×10^9), with 8.8% lymphocytes, 83.8% neutrophils. Plasma total cholesterol were slightly elevated (TC) with a normal Triglyceride level (TG). Electrolytes, CEA, CA-199, Lactate Dehydrogenase (LDH), liver and renal biochemical parameters are in normal range. Abdominal Ultrasound (US) didn't suggest any gallstones. He was diagnosed as acute pancreatitis. After standard treatment for pancreatitis, he relieved from abdominal pain.

After his epigastrium pain resolving, the patient's thyroid tumor and lymph nodes drew up our attentions. Thyroid tests firstly were within normal range. Cervical ultrasound revealed multiple solid hypoechoic masses with calcification in both side of thyroid gland that were categorized as ACR-TR 3 to 4 kinds. Thyroid CT showed that thyroid gland diffusely enlarged along with abnormal density and multiple solid nodules and cervical lymphadenopathies.

After a series of preoperative examination, on August 10th, 2021, the patient was performed on thyroidectomy. The biopsy of the thyroid tumor and cervical lymphadenopathies suggested that the thyroid tumor and nearby lymph nodes was diffusely invasive by medium-sized lymphoid cells (Figure 1A, 1B), which had red-stained cytoplasm and crowed nuclei with hyperchromatism and conspicuous karyokinesis (Figure 1C, 1D), conformed to DLBCL eventually. The immunohistochemical staining analysis of the tumor and lymphadenopathies presented that the lymphoblast were positive for CD20, CD79a, Bcl-6, Vimentin, Ki-67 (about 60%); partly positive for CD3; negative for CD5, CD10, CD117, CD30, CK, TTF-1, MUM-1. Bone marrow biopsy showed evidence of bone marrow involvement by the diffuse large B-cell lymphoma. The result of the

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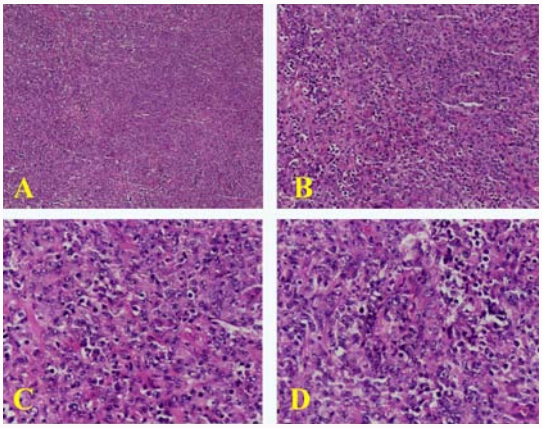

Figure 1(A-B): Medium-sized lymphoid cells diffuse infiltration in thyroid tumor and nearby lymph nodes (A, HE x40), (B, HE x100); **(C-D):** Typhoid cells were of red-stained cytoplasm and crowed nuclei with hyperchromatism and conspicuous karyokinesis (HE x200).

Fluorescence *in situ* Hybridization (FISH) indicated that tumor cells were negative for the rupture and rearrangements of Bcl-2, Bcl-6 and C-MYC gene. The cytogenetic analysis of bone marrow presented a regular karyotype 46, XY. Later, The man received a total body PET-CT examination, which showed that pancreas was diffusely invaded and abnormally metabolically active (SUVmax 44.3) (Figure 2b), the residual thyroid tissue also metabolized (about 43 mm × 68 mm, SUVmax 43.5) hypercritically and invaded the left thyroid cartilage and trachea (Figure 2a). In addition, heart ventricle (about 43 mm × 40 mm, SUVmax 27.9) and left renal parenchyma (about 21 mm × 16 mm, SUVmax 27.9) were displayed active metabolism due to lymphoma infiltration (Figure 2c). The patient was diagnosed with DLBCL, subtype GCB, with Ann Arbor stage III and International Prognostic Index of 3.

Then, the patient followed to receive R-CHOP regiment (rituximab, cyclophosphamide, pirarubicin, vincristine and prednisolone) for four courses. The chemotherapy process went well without serious complications. A repeat PET-CT after 4 cycles of R-CHOP displayed marked reduction in size of pancreas and residual thyroid tissue, radioactive avidity of them as well as other abnormal-metabolical organs like heart ventricle and left renal parenchyma returned down back to normal level (Figures 2A-2C). Now, the patient is still receiving R-CHOP regimen therapy. The effect of the treatment has been shown initially but the long-term therapeutic evaluation needs further observation and research.

Discussion

Diffuse Large B Cell Lymphoma (DLBCL) is the most common subtype of Non-Hodgkin Lymphoma (NHL), which accounts for approximately 25% of NHL cases. DLBCL patients usually behave painless lymphadenectasis of neck, 30% of whom may suffer from systemic "B" symptoms (fever, weight loss, drenching night sweats) [1]. There are about 30% cases of DLBCL arise from extranodal organs, most commonly gastrointestinal tract, bone marrow and skin [2]. The international Prognostic Index (IPI) has been used to assess the prognosis of DBLCL by age, clinical symptoms and laboratory data. With the development of Next-Generation Sequencing (NGS), more detail molecular mechanisms of lymphoma are elucidated and the benefit of rituximab immunochemotherapy is affirmed. The enhanced IPI in 2016, which reevaluates the criterion of DLBC's age and LDH, has suggested the significance of lymphomatous involvement in extranodal major organs (like CNS, bone marrow, gastrointestinal tract liver, or lung) as a strong prognosis factor [1]. Non-Hodgkin lymphoma frequently encroaches extranodal sites. Secondary involvement of pancreas by NHL is rare, being found in only 0.2% to 2% of patients at presentation [3]. The influence of other rare extranodal organs invasion like pancreas needs more records and study.

As the rapidly developing molecular technology, Gene Expression Profiling (GEP) has been used for distinguishing Germinal Center B-cell (GCB) of better prognosis, Activate B-Cell (ABC) of relatively poor prognosis and unclassifiable signatures in DLBCL [4]. In 2016, the World Health Organization (WHO) permit using immunohistochemistry for CD10, BCL2, MUM1, MYC and BCL6 or similar schemas to differentiate DBLCL to GCB subtype or ABC phenotype. However, when B-cell lymphoma encounters with MYC plus the translocations and/or rearrangement of BCL2 and/or BCL6, which is regarded as Double Hit Lymphoma (DHL) also considered of high-risk tendency [5,6]. Despite the GCB and ABC cells are not directly related to extanodal organs invasion, a statistical study from Thomas A. Ollila found that ABC cells were more enrich in lymphomas in specific extranodal sites in contrast to GCB cells [2]. In our reported case, the patient's FISH result was negative for C-MYC, Bcl-2 and Bcl-6 gene variation. He is grouped into GCB type that maybe predicts a relative favorable chemotherapy response and

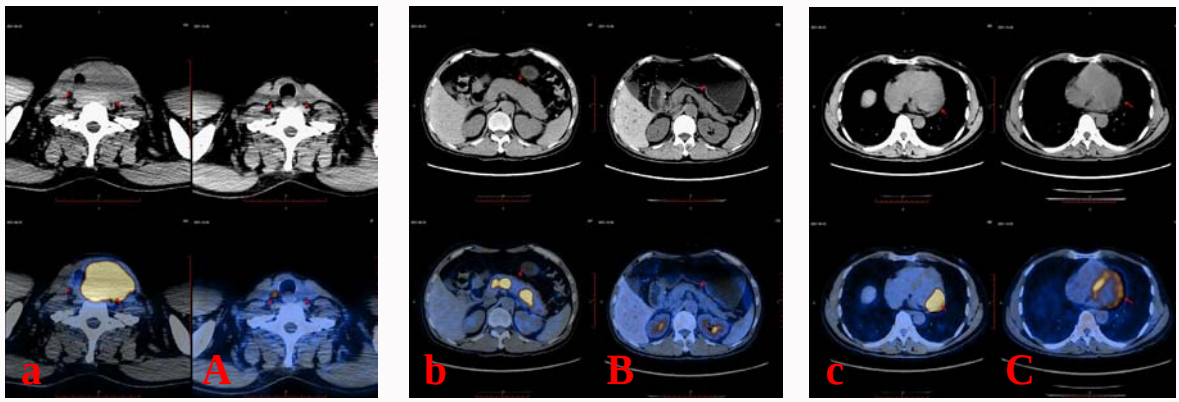

Figure 2(a-c): The PET-CT revealed abnormal hypercritical metabolism of residual thyroid, pancreas and heart ventricle respectively at diagnosis on August 23, 2021; (A-C): The PET-CT revealed respectively the lesion of pancreas, residual thyroid and heart ventricle had greatly reduced or even disappeared after 4 courses of R -CHOP regimen therapy.

prognosis to some degree.

DLBCL some extranodal involvements are common, and the reasons of multiple Extranodal Involvement (ENI) are still under investigation by scientists. DLBCL counts 50% of primary thyroid lymphomas that is strongly associated with autoimmune (Hashimoto) thyroiditis [7]. In Ali SZ' pathological statistical report, they found that chronic, antigenic stimulation of lymphocytes in Hashimoto could induce the synthesis of tumor compounds, such as Cyclooxygenase-2 (COX-2) and Forkhead box P3 (FOXP3), which has been detected in both thyroid epithelial neoplasms and Hashimoto [8,9]. DLBCL's pancreas invasions are even rarer. It happens that Alay Tikue et al. [10] reported a pancreatic DLBCL case also presenting as acute pancreatitis in 2020. In their reported case, the patient was complains of vomiting and serious epigastric abdominal pain, his pathology showed the diagnosis of DLBCL and achieved remission after 6 cycles of R-CHOP chemotherapy. More and more data suggest that there are divergent biological behaviors in extranodal DLBCL. According to Rong Shen et al. [11] a large patient cohort and genomic data, in addition to the bone marrow, CNS, liver and lungs defined by NCCN-IPI, lymphoma invasion of spleen, kidney/adrenal glands and bone, which are relate to prevalent ABC phenotype and MYD88/CD19 B-mutated genotype, are connected to inferior prognosis. In contrast, Gastrointestinal tract (GI) and thyroid DLBCL lack MYD88 mutations. As the most common extranodal sites, GI involvement show comparatively favorable prognosis.

Now, except for lymphocyte itself, the Tumor Microenvironment (TME) also has been a hot topic relate to lymphoma progression. TME is based on the interactions among immune cells, extracellular matrixes, inflammatory and stromal elements, which play an accelerating role in immune evasion, tumor spread and vasculogenesis [12,13]. Their impacts on extranodal sites involvement in DLBCL should be further researched.

Conclusion

A case of a DLBCL patient presenting as acute pancreatitis and the divergent biological behavior in extranodal DLBCL involvements are discussed in this paper. The possibility of DLBCL should be reminded when distinguishing a patient presenting as acute pancreatitis with no obvious cause or poor therapeutic effect despite standard therapy.

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