

Mikulicz's Syndrome: A case report

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Abstract: Mikulicz's syndrome is characterized by the symmetrical enlargement with lymphocytic infiltrations of the parotid salivary glands and the lacrimal glands. Its common causes are lymphoma, and other autoimmune diseases. So far, it has been rarely reported therefore we additionally report one case in a Thai patient. He was a 65-year-old Thai presenting with the gradual enlargement of multiple masses at both eye brows, both parotid glands and both sides of the cervical lymph nodes within a few months without local or constitutional symptoms. The size of the masses varied, 2-3 cm, firm consistency, no fluctuation, and no tenderness. No lymph nodes at other parts of the body were found on the physical examination, the ultrasonography of the upper abdomen and the chest film except the small pretracheal lymphadenopathies found on the computed tomography of the chest. The blood tests for anti-SSA and anti-SSB antibodies were found negative. The microscopic pathology of the cervical lymph node was shown to be the atypical lymphoid hyperplasia, suggestive of Hodgkin disease, mixed cellularity. He was diagnosed as having Mikulicz's syndrome, with an underlying Hodgkin's lymphoma, mixed-cellularity at least stage IIA. After the multi-drug chemotherapy, all masses disappeared within only one course. Because this case had no anti-SSA, anti-SSB antibodies and no kerato-conjunctivitis sicca, it seemed to support the proposal that Mikulicz's syndrome and Sjogren's syndrome are different entities.

Key Words: Mikulicz's Syndrome, Hodgkin's disease

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Mikulicz's syndrome มีลักษณะจำเพาะคือการมีต่อมน้ำลายพาโรติดและต่อมน้ำตาโตขึ้นอย่างช้า ๆ และสมมาตรเนื่องจากมีเซลล์เม็ดน้ำเหลืองแทรกซึมเข้าไปสาเหตุที่พบบ่อยคือโรคมะเร็งต่อมน้ำเหลืองและโรคกลุ่ม autoimmune อื่น ๆ จนปัจจุบันนี้โรคนี้ก็ยังพบน้อยจึงเขียนรายงานนี้ผู้ป่วยเป็นชายไทยอายุ 65 ปีมีก้อนเนื้ออกที่ทางซ้ายทั้ง 2 ข้างต่อมน้ำลายพาโรติดทั้ง 2 ข้าง และต่อมน้ำเหลืองที่คอทั้ง 2 ข้างภายในไม่กี่เดือนก่อนเหล่านี้โตช้า ๆ โดยผู้ป่วยไม่มีอาการทั้งเฉพาะที่และอาการทั้งระบบขนาดของก้อนเนื้อเหล่านี้ประมาณ 2-3 เซนติเมตร ค่อนข้างแข็งไม่มีจุดนุ่มกดไม่เจ็บไม่พบต่อมน้ำเหลืองโตในที่อื่น ๆ ของร่างกายไม่ว่าจะโดยการตรวจร่างกาย การตรวจช่องท้องส่วนบนด้วยเครื่องสะท้อนคลื่นเสียงความถี่สูงและการเอกซเรย์ธรรมดาของปอด ยกเว้นมีต่อมน้ำเหลืองเล็ก ๆ หนาหลอดลมที่พบโดยเอกซเรย์คอมพิวเตอร์ของทรวงอกตรวจเลือดหาภูมิ anti-SSA และ anti-SSB แล้วไม่พบตรวจชิ้นเนื้อจุลพยาธิวิทยาของต่อมน้ำเหลืองจากคอพบว่าเป็น atypical lymphoid hyperplasia, suggestive of Hodgkin disease, mixed cellularity จึงให้การวินิจฉัยว่าเป็น Mikulicz's syndrome โดยมีโรคนำเดิม คือ Hodgkin's disease, mixed cellularity at least stage IIA หลังจากได้ยาเคมีชุดที่มียาหลายขนาน ปรากฏว่าก้อนต่าง ๆ ยุบเกลี้ยงเพียงได้ยาเคมีชุดแรกเท่านั้นเนื่องจากผู้ป่วยรายนี้ไม่มี anti-SSA, anti-SSB และไม่มีอาการ keratoconjunctivitis sicca จึงดูเหมือนว่าผู้ป่วยรายนี้สนับสนุนข้อเสนอก่อนที่ว่า Mikulicz's Syndrome กับ Sjogren's syndrome เป็นโรคคนละกลุ่มกัน

คำสำคัญ: Mikulicz's Syndrome, Hodgkin's disease

Introduction

Mikulicz's syndrome is a rare condition of the parotid salivary glands and the lacrimal glands characterized by the symmetrical lacrimal, parotid and submandibular glands enlargement with the lympho- cytic infiltrations. The typical manifestation is the progressive enlargement of the tumors at both upper eyelids, both parotid glands without pain. Its common causes are lymphoma, Hodgkin's disease, tubercu- losis, Sjogren's syndrome, SLE, etc. If the underlying causes cannot be identified, it will be called Mikulicz's disease or benign lymphoepithelial lesion. The diagnosis of Mikulicz's disease is based on the com-bination of symmetrical and persistent swelling

in more than two lacrimal and major salivary glands and the prominent mononuclear infiltration of the glands and the exclusion of other diseases that present with glandular swelling^(1,2).

The patients with this disease hardly have constitutional symptoms such as weight loss or fever. And all tumor masses are always firm and non-tenderness⁽³⁾.

Mikulicz's disease is proposedly the different entity from Sjogren's syndrome because the patient with Mikulicz's disease always has elevated serum immunoglobulin G-4⁽⁴⁾ and negative test for anti-SSA/SSB antibodies. Histopathologically, only Mikulicz's disease has prominent infiltration of IgG4-positive

plasmacytes into the lacrimal and salivary glands and responds well to corticosteroids⁽¹⁾. Moreover, the tissue is helpful for excluding other diseases that present with glandular swelling, such as sarcoidosis and lymphoproliferative disease⁽⁵⁾.

After the syndrome was firstly described by Jan Mikulicz-Radecki, the Polish surgeon, in 1888, it has been sporadically reported since then⁽⁶⁾. In Thailand, it has been hardly found so far. Here we present one case.

Case Report

A 65-year-old Thai man presented with progressive enlargement of multiple masses at both eye brows, both parotid glands and both sides of cervical lymph nodes within a few months. All these masses gradually enlarged without local symptoms. He did not have any constitutional symptoms. On the physical examination, he had multiple masses at the lateral ends of both eye brows, both parotid glands and both sides of the cervical nodes, size 2-3 cm, globular, firm, smooth, no fluctuation, no tenderness, movable, normal covering skin. He did not have lymphadenopathy at other parts, no hepatosplenomegaly.

Laboratory tests: Hb 12.2 g%, Hct 36.5 %, WBC 22,600/mm³, platelet 170,000/mm³ N 91.9 % L 2.7 % M 5.4 %, ESR 98/hr. The HIV antigen/antibody, HBsAg, anti-HCV were all negative. The anti-SSA (anti-Ro) and anti-SSB (La) antibodies were negative but anti-cytoplasmic antibody and ANA were positive, fine speckle titer 1:80. Serum albumin 3.4 g%, globulin 6.3 g%, creatinine 1.49 mg%, P 2.6 mg%, BS 159 mg%.

The ultrasonography of the abdomen showed no lymphadenopathy. But the computerized tomography of the chest showed the multiple small pretracheal lymphadenopathies. Biopsy of the left cervical node showed the diffuse effacement of lymph node by a proliferation of large atypical cells with round nuclei,

prominent nucleoli and scant cytoplasm. Some of them show binucleation. They are scattered among mixed inflammatory cells including lymphocytes, plasma cells and a few eosinophils. Only few residual lymphoid follicles are observed. Immunostaining of these large transformed lymphocytes mark with LCA, CD20, sparse CD30, CD57, do not mark with CD3, CD15, EMA, EBV (LMP). Conclusion was reactive lymphoid hyperplasia with immunoblastic proliferation.

Within 6 months, the patient was still well along with all persistent masses. The laboratory tests were all repeated. Most of them were similar except for the globulin which was rising to 10.5 g%. The other tests were additionally performed: LDH 389 IU, AST 41 IU, ALT 12 IU, alkaline phosphatase 100 IU, CK-MB 2.4 ng/mL, troponin-I 0.0, FBS 94 mg%. The serum immuno-electrophoresis was normal. Urinalysis was normal and urine Bence-Jones's protein was negative.

The chest film showed unremarkable study and the bronchial washing cytology was found negative for malignant cell.

The cervical lymph node biopsy was repeated and the pathological diagnosis was atypical lymphoid hyperplasia, suggestive of Hodgkin disease, mixed cellularity.

The final clinical diagnosis was Mikulicz' syndrome with an underlying Hodgkin's disease, mixed cellularity, stage at least II A and he was treated with multi-drug chemotherapy and responded well, all masses completely disappeared within 1 course.

Discussion

Our patient was diagnosed as having Mikulicz' syndrome with an underlying Hodgkin's disease and the diagnosis of Sjogren's syndrome was much less likely because he did not have the complaint of eye symptoms while the anti-SSA (Ro) and anti-SSB

(La) antibodies were both negative⁽⁷⁾. So Mikulicz's syn-drome and Sjogren's syndrome were considered the different entities by some authorities^(8,9).

Nowadays, Mikulicz's syndrome is repeatedly proved to be the multi-organ involvement or the systemic manifestation of the immunoglobulin G4 positive plasma cell disease and there is frequently some infiltration of IgG4 positive plasma cells⁽¹⁰⁻¹³⁾. Our case has high serum total globulin (6.3 and then 10.5 g%) and the plasma cells infiltration with immunoblastic transformation in the tissue but the identification of IgG4 subclass cannot be performed in our institute.

Some authorities suggest Mikulicz's disease or Mikulicz's syndrome should not be used anymore because the original case which was reported by Mikulicz showed a microscopic field of one of the submandibular glands containing a uniform lympho-cytic infiltrate of centrocyte-like cells typical of MALT lymphoma⁽¹⁴⁾.

Mikulicz's syndrome may be found prior the manifestation⁽¹⁵⁾ or as the presentation of tumors particularly non-Hodgkin's lymphoma, Hodgkin's disease or leukemia⁽¹⁶⁾. For the first time, our case did not have lymphoma but later the cervical lymph node was pathologically proved to be Hodgkin's disease, leading to the treatment with combination of chemotherapy. Other diseases which should be differentiated in cases of Mikulicz's syndrome included the chronic inflammation, metastatic carcinoma⁽¹⁷⁾ and sarcoidosis⁽¹⁸⁾. In fact, the treatment and prognosis of Mikulicz's syndrome depend on the underlying diseases. If it is Mikulicz's disease, it will be highly responsive to corticosteroids⁽¹¹⁾.

Our patient has neither anti-SSA, anti-SSB antibodies nor kerato-conjunctivitis sicca, the diagnosis of Sjogren's syndrome is not possible⁽¹⁹⁾. It seemed to support the proposal that Mikulicz's syndrome and Sjogren's syndrome are different entities although

their pathologies looked similar⁽⁸⁾.

Our case has never developed any complication of Mikulicz's syndrome such as autoimmune pancreatitis, retroperitoneal fibrosis, tubulointerstitial nephritis, autoimmune hypophysitis, and Riedel's thyroiditis⁽⁵⁾.

Conclusion

A 65-year-old Thai man was clinically diagnosed as Mikulicz's syndrome because of the enlargement of bilateral lacrimal, parotid and the cervical lymph nodes. The pathology of the lymph nodes were found to be hyperplasia and later Hodgkin's disease. And he responded well to chemotherapy. All masses disappear within one course.

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