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Immunoproliferative Small Intestinal Disease : Report of Two Cases

Likhasit Sangluthong[1]
Somchai Insiripong[1]
Naruda Jiragalwasan[2]

Abstract Immunoproliferative small intestinal disease (IPSID) or alpha heavy chain disease is a subtype of mucosa-associated lymphoid tissue (MALT) lymphoma that occurs almost exclusively in the Middle East and Mediterranean basin. It tends to be a disease of young males. Herein, we report two unrelated Thais with IPSID who have never visited the Middle East. The first case was a 50-year-old woman presenting with generalized abdominal pain for a few months, passing watery stool every other day, without blood or mucus. Her blood test showed pancytopenia and hyperglobulinemia. Colonoscopy revealed a large half-circumferential clean based ulcer, with friable surrounding tissue. The cecum microscopic pathology was consistent with IPSID. The stool had no parasite. She was treated with right-half colectomy, prednisolone, danazol, tetracycline, and omeprazole. The patient survived a further year and 9 months. The second case was a 72-year-old man presenting with acute abdominal pain due to gut obstruction for 3 days. Exploratory laparotomy was immediately performed for a part of the small bowel that was affected for resection. Microscopic pathology was compatible with IPSID. His blood tested positive for latent syphilis but normal serum globulin. After the operation, he was treated with tetracycline and cyclophosphamide, and he survived for a further two years. These two cases were IPSID diagnosed outside the Middle East and Mediterranean Region; the ages of the cases were not young, at 50 and 72 years. Regarding the site of involvement, the colon in the first case was considered an unusual site for IPSID. As for infection that might contribute to the occurrence of IPSID, there was no infective diarrhea in the first case and only latent syphilis in the second case. *(Thai Cancer J 2017;37:1-6)*

Keyword: IPSID, gastrointestinal lymphoma, small intestinal disease

[1]Department of Medicine, [2]Department of Pathology, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, 30000

Immunoproliferative Small Intestinal Disease: รายงานผู้ป่วย 2 ราย

โดย **ลิขสิทธิ์ แสงลู่ทอง[1] สมชาย อินทรศิริพงษ์[1] นฤดา จิรกาลวสาน[2]**

[1]กลุ่มงานอายุรกรรม [2]กลุ่มงานพยาธิวิทยา โรงพยาบาลมหาราชนครราชสีมา จ. นครราชสีมา 30000

บทคัดย่อ โรค immunoproliferative small intestinal disease (IPSID) หรือ โรค alpha heavy chain เป็นชนิดย่อยของมะเร็งต่อมน้ำเหลืองแบบ mucosa associated lymphoid tissue (MALT) เกือบทั้งหมดของผู้ป่วยพบในตะวันออกกลางและแถบทะเลเมดิเตอร์เรเนียน ผู้ป่วยส่วนมากเป็นผู้ชายอายุน้อย ในบทความนี้เป็นรายงานผู้ป่วย 2 รายที่พบในคนไทยและไม่เคยไปตะวันออกกลาง รายที่ 1 เป็นหญิงอายุ 50 ปี มีอาการปวดท้องถ่ายเหลวไม่มีมูกเลือดเกือบทุกวันเป็นเวลา 2-3 เดือน ตรวจเลือดพบ pancytopenia และ hyperglobulinemia ส่องกล้องทางทวารหนักพบว่า ลำไส้ใหญ่มีแผลเปื่อยกว้างประมาณครึ่งหนึ่งของเส้นรอบวงลำไส้ ลักษณะทางจุลพยาธิของ caecum เข้าได้กับ IPSID ตรวจอุจจาระไม่พบพยาธิ ผู้ป่วยได้รับการรักษาด้วยการผ่าตัด right half colectomy, prednisolone, danazol, tetracycline, omeprazole ผู้ป่วยยังคงมีชีวิตอีก 1 ปี 9 เดือน ส่วนรายที่ 2 เป็นชายอายุ 72 ปี มีอาการปวดท้องเฉียบพลันเนื่องจากลำไส้อุดตัน 3 วัน ผู้ป่วยได้รับการผ่าตัดฉุกเฉินด้วยการตัดลำไส้เล็กออกบางส่วน ผลทางจุลพยาธิพบว่า เข้าได้กับ IPSID ตรวจเลือดพบซิฟิลิสแฝง ระดับ globulin ปกติ หลังผ่าตัดผู้ป่วยได้รับการรักษาด้วยยา tetracycline และ cyclophosphamide ผู้ป่วยมีชีวิตต่อมาอีกเป็นเวลา 2 ปี ผู้ป่วยทั้ง 2 รายนี้เป็นโรค IPSID ที่พบนอกเขตตะวันออกกลางและแถบเมดิเตอร์เรเนียน อีกทั้งมีอายุไม่น้อย (50 ปีและ 72 ปี) ส่วนตำแหน่งที่พบโรคในผู้ป่วยรายแรกนั้นเป็นลำไส้ใหญ่ ซึ่งถือเป็นตำแหน่งที่พบน้อยของโรค IPSID สำหรับการติดเชื้อที่อาจจะเกี่ยวข้องกับ IPSID นั้น ผู้ป่วยรายแรกไม่พบการติดเชื้อในลำไส้ ส่วนรายหลังพบเฉพาะการติดเชื้อซิฟิลิสระยะแฝง *(วารสารโรคมะเร็ง 2560;37:1-6)*

คำสำคัญ: IPSID มะเร็งต่อมน้ำเหลืองของทางเดินอาหาร โรคลำไส้เล็ก .

Introduction

The immunoproliferative small intestinal disease (IPSID) or alpha heavy chain disease, Mediterranean lymphoma, diffuse small intestinal lymphoma is a specialized subtype of mucosal associated lymphoid tissue (MALT) lymphoma (or extranodal marginal zone B-cell lymphoma of MALT type in the REAL/WHO classification) which is the most common primary gastrointestinal lymphomas worldwide. IPSID occurs almost exclusively in the Middle East and Mediterranean basin. It is often associated with relatively poor sanitation and is characterized by the synthesis of an alpha heavy chain paraprotein. It tends to be a disease of young adults, and also shows a slight male predominance[1].

IPSID-type intestinal GI lymphomas generally present as a diffuse infiltrating lesion, sometimes resembling cobble stoning, with a predilection for the proximal small intestine. As in gastric lymphomas, mesenteric lymph node involvement and/or direct extension into adjacent structures is a feature of advanced disease. This disease with benign or intermediate grades, may respond well to the treatment directed against Campylobacter jejuni infection, such as oral tetracycline but for malignant grade, it needs aggressive chemotherapy, like CHOP regimen[2].

The patients with IPSID may clinically present with generalized abdominal pain, chronic diarrhea for a few months or years, malabsorption, severe weight loss and/or malnourished, clubbing of fingers and ankle edema[3].

In Thailand, as other Southeast Asian countries, IPSID is not common[4,5] and herein we report two cases of IPSID proved by the immunophenotype study.

Report of Cases

Case 1: A 50-year-old Thai woman presented with generalized abdominal pain for a few months. During this time, she always passed watery stool every other day, no blood or mucus. She also had low graded fever and significant weight loss. The physical examination revealed just only pallor, no jaundice, no hepatosplenomegaly. The chest film was unremarkable. The computerized tomography of abdomen showed the thickened bowel wall at the descending colon, the inflammation was considered.

Blood tests: Hb 7.8 g%, WBC 1400/mm^3, N 12 %, L 60 %, M 19 %, platelet 36,000/mm^3, albumin 2.9 g%, globulin 6.1 g% with normal immune-electrophoretic pattern, CEA 0.92 (normal 0-5 mcg/l). Stool examination did not show WBC or any parasite. Colonoscopy revealed one large half-circumferential clean based ulcer, with friable surrounding tissue.

The cecum showed an ulcer made of inflamed granulation tissue and diffusely infiltrated by plasma cells with few lymphocytes. The plasma cells densely occupied the lamina propria. Extension of the muscular wall was also noted. Both resected margins and appendix were unremarkable. The regional lymph nodes showed reactive change. The immunohistochemical study showed diffuse positive CD38 and VS38c. CD3 and CD20 were sparsely positive in the small lymphocytes. The pathology was consistent with IPSID.

The bone marrow showed moderate hypercellularity (cell : fat ; 90 : 10), consisted of all series of hematopoietic cells with normal maturation, no granuloma, no ringed sideroblast and the immunostaining showed few scattered CD34+ immature cells and rather equal T and B cells. Stainings with Glycophorin C and CD138 highlight erythroid precursors and plasma cells, respectively. No evidence of light chain restriction was seen in these plasma cells.

Treatment consisted of right half colectomy followed by oral prednisolone, danazol, tetracycline, omeprazole. The patient survived for a further year and 9 months.

Case 2: A 72-year-old Thai man presented with acute abdominal pain due to gut obstruction

for 3 days. His status was bed ridden due to CVA. The exploratory laparotomy was immediately performed for a part of the small bowel that was affected for resection and end-to-end anastomosis.

Laboratory tests: Hb 11.8 g%, WBC 6000/mm^3, platelet 276,000/mm^3, BUN 7.0 mg%, cholesterol 206 mg%, normal liver function tests, albumin 3.9 g%, globulin 3.6 g%, FBS 76 mg%, ESR 109 mm/hr, VDRL 1:2, TPHA reactive, Hb electrophoresis: AE, Hb E 24.3 %.

The microscopic pathology showed distortion and destruction of the intestinal wall by the abnormal dense lymphoid and plasma cells. The cells were lymphoplasmacytic cells or centrocyte-like cells with mature plasma cells admixed by increasing numbers of large immunoblasts and neutrophils. The cells involved the mucosa extending to deep muscular layer and subserosa at some points. Some cells exhibited the marked nuclear atypia, bizarre configuration of cytoplasmic organelles and asynchronous nuclear and cytoplasmic maturation. No definite lymphoepithelial lesion was found to indicate neoplastic transformation. The superficial erosion and ulceration were seen in many areas. The regional lymph nodes showed reactive hyperplasia. The histologic features were compatible with the IPSID and supported by mixture of CD3 and CD20.

After operation, he was treated with tetracycline and cyclophosphamide and he survived for a further two years.

Discussion

Our cases were diagnosed as having IPSID by the hematopathologist based on the microscopic pathology of the surgical specimens stained with the immunohistochemical method[6].

The first case presented with chronic diarrhea with generalized abdominal pain that is the most common presenting symptom of IPSID in general[7], whereas the second case presented with acute gut obstruction that has been found in only 26% of the Asian patients with IPSID[8]. However the gut obstruction was not mentioned in Thai patients with IPSID in the former studies[4,5].

Actually IPSID has its highest incidence in the third decade of life in both sexes. In India, mean age of the patients is 29.8 $\pm$ 11.8 years (range 17-53 years)[9] but the ages of our patients are older particularly the second case.

So far, the well-known associated factor of IPSID is enteritis[10]. Chronic diarrhea occurred in the first patient, but neither the white blood cell nor the parasite was found in the stool. The second case had no diarrhea but latent syphilis instead. In the retrospective review, there was no association between syphilis and cancer of the

urinary bladder or prostate gland[11]. The association between syphilis and IPSID has never been mentioned although syphilis may mimic cutaneous lymphoma[12] or induce lymphadenopathies that are pathologically misdiagnosed as lymphoma[13].

The main part of the intestine that is commonly involved by IPSID is the small intestine particularly the jejunum[8] or duodenum[2]. In our patients, the lesion of IPSID was found in the small intestine of the second case but in the cecum of the first case, the very unusual site for IPSID[14]. In fact, the large bowel is considered the unusual site for any primary non-Hodgkin lymphoma (NHL) accounting for 10-20 % of all GI lymphoma as compared with the stomach which comprises only 0.1-0.5 % of all colonic malignancies. The more common subtypes of lymphoma of the large bowel is the large B-cell lymphoma 47-81 %, in contrast, extranodal mucosa-associated lymphoid (MALT) lymphoma and others are less commonly found[15].

The important treatment for IPSID is tetracycline with or without chemotherapy[2]. Our cases were also treated with tetracycline and other symptomatic cares. About the survival of the victims of this disease, the overall remission rate is 90 $\pm$ 12 % at two years and 67 $\pm$ 25% at three years[16]. And our patients could survive within the interval nearly similar to the general survival time.

Conclusion

Two Thai patients were diagnosed as having the immunoproliferative small intestinal disease (IPSID) based on the immuno-pathological findings. The lesions were found involving cecum in the first case and small intestine in the second. They were treated with the surgical removal and tetracycline and survived for a further around two years.

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