Extensive juvenile xanthogranuloma with autoimmune lymphoproliferative syndrome: report of a case and review.

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ABSTRACT:

CHANDAYANI N*, PHOTIA A, TRIVAREE C**, THITTHIWONG P*** EXTENSIVE JUVENILE XANTHOGRANULOMA WITH AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME: REPORT OF A CASE AND REVIEW. THAI J DERMATOL 2017; 33: 258-266.**

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Juvenile xanthogranuloma (JXG) is an unusual disorder belonging to the group of non-Langerhans cell histiocytosis. Most clinical presentation affects only the skin, but extracutaneous manifestations are not uncommon such as ocular, lung and hematologic involvement. We reported a 6 months old girl presented with extensive lesions of JXG concomitant with thrombocytopenia and hemolytic anemia which finally diagnosed with autoimmune lymphoproliferative syndrome (ALPS). She was treated with intravenous immunoglobulin (IVIG), rituximab and mycophenolate mofetil (MMF). After 6 months of treatment, thrombocytopenia and anemia gradually returned to normal. The spontaneous regression of some skin lesions of JXG were observed after 1 year old. Clinical of ALPS were in remission. To our knowledge, there is no report in the English literature regarding the association between JXG and ALPS.

Key words: Juvenile xanthogranuloma, Autoimmune lymphoproliferative syndrome, Rituximab

บทคัดย่อ:

ณัชชา จันทะยานี*, อภิชาต โพธิอะ, ชาญชัย ไตรวารี**, ปาจรีย์ ฑิตธิวงษ์*** รายงานผู้ป่วยเด็กที่มีกลุ่มอาการผิดปกติ LYMPHOPROLIFERATIVE เกิดร่วมกับโรคผิวหนังชนิด JUVENILE XANTHOGRANULOMA และทบทวนวรรณกรรม วารสารโรคผิวหนัง 2561; 33: 258-266.**

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Juvenile xanthogranuloma (JXG) เป็นโรคที่มีความผิดปกติของ histiocyte ชนิด non-Langerhans cell ผู้ป่วยส่วนใหญ่แสดงอาการทางระบบผิวหนังเป็นหลัก แต่พบรายงานในระบบอื่นได้เช่น ตา ทางเดินหายใจ และระบบโลหิตวิทยา รายงานฉบับนี้นำเสนอผู้ป่วย JXG ที่มีปัญหาเกร็ดเลือดต่ำและซีด ผู้ป่วยได้รับการวินิจฉัยเป็น autoimmune lymphoproliferative syndrome (ALPS) ผู้ป่วยรายนี้ตอบสนองต่อการรักษาด้วย intravenous immunoglobulin (IVIG) และ rituximab ได้ผลดี ที่ผ่านมาพบว่ามีความสัมพันธ์ของ JXG กับมะเร็งทางโลหิตวิทยา แต่ยังไม่พบรายงานความสัมพันธ์กับภาวะ ALPS

คำสำคัญ: กลุ่มโรคฮีสติโอไซโตซิส, กลุ่มอาการผิดปกติ Lymphoproliferative

Introduction

Juvenile xanthogranuloma (JXG) is a non-Langerhans cell histiocytosis, affecting mostly in infants younger than 6 months of age with 70% occurring in the first year of life. The classical manifestation of JXG presents with asymptomatic, 0.5 to 2.0 cm, single or multiple, yellow to orange dome-shaped papules or

nodules with rubbery in consistency. The predilection sites are head, neck, upper trunk and extremities. Extracutaneous involvements are not uncommon, involving oculars, lungs, abdominal viscera, hematologic system and bony structures. Number of literatures show association between JXG, neurofibromatosis type 1 and juvenile myelomonocytic leukemia but other hematologic associations are rare, with only 12 reports described so far. We reported a case of extensive lesions of JXG concomitant with thrombocytopenia and hemolytic anemia which finally showed autoimmune lymphoproliferative syndrome (ALPS).

Case report

A 6-month-old girl presented with high grade fever, anemia and thrombocytopenia since 2 months old. She was a child of healthy parents with full-term delivery. At the age of 5 months, her mother noticed the eruptive asymptomatic, small yellowish papules on her face, upper trunk and extremities which progressively increased in number to more than 100 lesions. Her growth and developmental milestones were normal. Physical examination revealed high grade fever, anemia, hepatosplenomegaly. Dermatologic finding shows multiple discrete yellowish-orange papules, size 0.3 to 0.5 cm on face, scalp, trunk and extremities (Figure 1,2). There were no café-au-lait spots or other birth marks. Ophthalmologic examination was normal. Complete blood count showed, hemoglobin 10.8g/dl, hematocrit 31.5%, white blood cell 7,500/mm^3 (N29%, L57%, M7%, Eo7%) with platelets 14,000/mm^3. Peripheral blood smear showed microcytic, hypochromic red blood cell and also found microspherocyte. The direct antiglobulin test (DAT) was positive 3+. Transaminase, lactate dehydrogenase, bilirubin, blood urea nitrogen, and creatinine levels were normal. Serum immunoglobulin (Ig) levels were as follow: IgG 2,313mg/dl (700-1600), IgA 58mg/dl (70-400), and IgM 73mg/dl (40-230). Ultrasonography of the abdomen showed a homogeneous enlarged liver, a normal-sized gall bladder, and no bile duct enlargement. CT abdomen described enlarged liver (8.3 cm) with marked splenomegaly (7.4cm) when compare with age. The bone marrow aspiration showed hypercellular marrow with increased megakaryocytes without blast cells. Flow cytometry revealed elevated double-negative T-cells (DNTs); cell phenotype CD3+ /TCRα/β+ /CD4- /CD8-. She was diagnosed with autoimmune lymphoproliferative syndrome (ALPS).[1] Biopsy of the yellowish papule from dorsal of left hand confirmed nodular infiltration in upper dermis, composed of histiocytes, foamy histiocytes and Touton type giant histiocytes (Figure 3,4). The immunohistochemistry strained positive for CD68, but negative for protein S100 and CD1a. Then JXG was diagnosed.

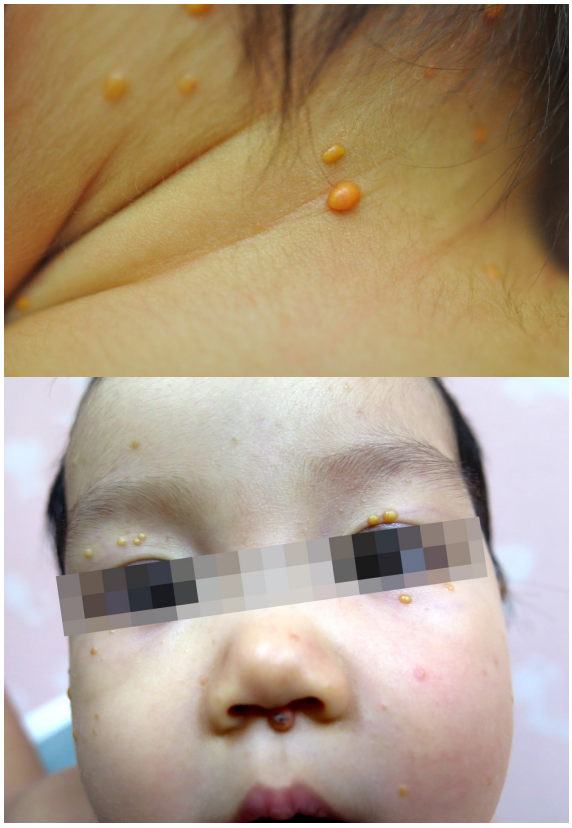

Figure 1,2 multiple scatter of yellowish to orange dome-shaped papules on neck and face area

The hematologists started the treatment of ALPS with 3 consecutive courses of intravenous immunoglobulin therapy (2 g/kg/dose), her clinical was improved. Four months later, thrombocytopenia and anemia reappeared, then rituximab (375 mg/m^2) was given monthly along with mycophenolate mofetil (MMF) that given twice daily orally at a dose of 600 mg/m^2.[2,2] After 6-months of this treatment, hemoglobin levels and platelet counts gradually returned to normal (183,000/mm^3). Spontaneous regression of JXG was observed after 6 months, starting at the head and neck regions follow by the trunk. After the age of 18 months, there was no new lesion of JXG occurred.

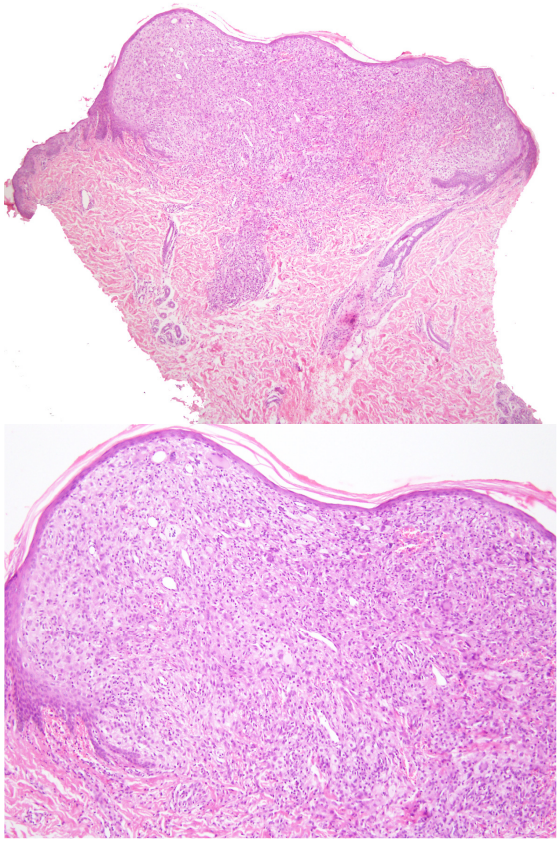

Figure 3,4 well-circumscribed nodular infiltration in upper dermis, composed of histiocytes, foamy histiocytes and Touton type giant histiocytes (4X), (10X)

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Table 1 Reported cases of Juvenile xanthogranulomatosis with hematologic involvement

No.	Age	Skin lesion	CALM	Hematologic	BM	Other visceral organ	Treatment	Outcome/duration follow up	References
1	2mth	Multiple	No	Anemia, Thrombocytopenia	Postitive*	Spleen, liver, heart	VP16, VBN	Alive, regression(+20mth)	6
2	at birth	Multiple	No	Anemia, Thrombocytopenia	Postitive*	Spleen, liver,pancreas	VP16, DXM	Death of disease(+29day)	7
3	at birth	Multiple	Yes	Anemia, Thrombocytopenia	JMML	Spleen, liver	CMT	Death of disease(+3.5year)	8
4	3mth	Multiple	No	Anemia, Thrombocytopenia	Proliferation BM	Spleen, liver	VBL, PDN	Alive, with disease(+6mth recur)	9
5	5year	Multiple	No data	Anemia, Thrombocytopenia	ALL	Spleen, liver, lung, kidney, GI	COALL(ALL regimen)	Death of disease(+252day)	10
6	8mth	Multiple	No data	Anemia, Thrombocytopenia	JMML	Spleen, liver	BMT	Alive with disease(+40day)	11
7	6wk	No	No data	Anemia, Thrombocytopenia	Postitive*	No extrahematologic site	VCR	Alive with disease(+8mth)	12
8	8mth	Multiple	No	Anemia, Thrombocytopenia	Postitive*	Spleen, liver, intestine	VBL, PDN	Progression	13
							Ara-C, 2CDA	Alive with disease free(+18mth)	
9	2mth	Multiple	No	Anemia, Thrombocytopenia	Postitive*	Spleen, liver, intestine	VBL, PDN	Progression	
							Ara-C, 2CDA	Alive with disease free(+12mth)	
10	2mth	No	No	Anemia, Thrombocytopenia	Postitive*	Liver	VBL	No response	14
							VP16	Alive with disease free(+2year)	
11	2week	Multiple	No	Anemia, Thrombocytopenia	Postitive*	Spleen, liver	PDN	Alive with disease free(+17mth) both twin	15
12	at birth	Multiple	No	Anemia, Thrombocytopenia	Postitive*	Spleen, liver	CsA	Progression	16
							VBL, PDN	Alive with disease free(+26mth)	
13	2mth	Multiple	No	Anemia, Thrombocytopenia	ALPS	Spleen, liver	IVIG, Rituximab	Alive, regression(+2year)	Our case

CALM: café au lait macule; BM, bone marrow; JMML, juvenile myelomonocytic leukemia; VP16,Etoposide; VBL,Vinblastine; VCR,Vincristine; Ara-C,Cytarabine; CsA,Cyclosporine; PDN,Prednisolone; DXM, Dexamethasone; BMT,bone marrow transplant

*Bone marrow positive means histiocytic cells infiltrate

Discussion:

JXG is the most common type of non-Langerhans cell histiocytic proliferative disorders. The natural history of JXG usually runs benign course with gradual regression within 3 to 6 years. Individual lesion of JXG may resolve completely or leave a residual atrophic scar or hyperpigmented macule. In 2003, Dehner LP reported 174 cases of JXG in children, which 67% of cases had solitary skin lesion and only 7 % had multiple skin lesions. In addition, 4% of cases had multiple skin lesions with other system involvement including lung, liver, spleen, kidney, brain, adrenal gland, lymph nodes, and bone.[3] Most of the literatures reported the ocular involvement as the complication of JXG including spontaneous hyphema, glaucoma and blindness, especially the periocular JXG lesions.[4] Systemic JXG was defined in the case having more than one affected organ, which associated with significant complications and requiring aggressive medical treatment.[5] The treatment of systemic JXG derives from those used in Langerhan cell histiocytosis including steroids and vinblastine.

Hematologic involvement in JXG is rare. Only 12 reported cases were documented with bone marrow involvement. Table I shows reported cases of JXG with hematologic association. Eight children had histiocytes infiltrated bone marrow

(case No. 1, 2, 7, 8, 9, 10, 11, 12) and all were treated with systemic chemotherapy. Only one out of eight patients died of disease due to liver failure (case No. 2). There were 3 children reported blast cell infiltrated bone marrow (juvenile myelomonocytic leukemia in case No. 3, 6 and acute lymphoblastic leukemia in case No. 5). Our patient's bone marrow was found neither histiocyte nor blast cell infiltration and flow cytometry showed elevated double-negative T-cells (DNTs); cell phenotype CD3+ /TCRα/β+ /CD4- /CD8-. Furthermore, the high level of immunoglobulin G and hemolytic anemia in this patient fit the diagnostic criteria of ALPS.[1]

ALPS is a disorder of abnormal lymphocyte survival caused by dysgranulation of the FAS apoptotic pathway resulting in excess $\alpha\beta$ + CD3+CD4−CD8− called double negative T (DNT) lymphocytes that accumulated in lymph node, spleen and peripheral blood. Clinical presentation of ALPS shows lymphadenopathy, hepatosplenomegaly and multilineage cytopenias from splenic sequestration and/or autoimmunity. ALPS can be associated with various types of malignancies especially Hodgkin or non-Hodgkin lymphomas including solid tumors of thyroid, skin, heart and lung. Main treatment of ALPS was to control primary disease manifestations and complications including lymphoproliferative disorder and autoimmune cytopenias by use immunosuppression. Initial treatment includes high-dose corticosteroid and intravenous immunoglobulin (IVIG) then other steroid sparing agents that have been trialed in refractory ALPS as rituximab, mycophenolate mofetil (MMF) and sirolimus. Rituximab has been used in many autoimmune diseases including autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura. For ALPS, rituximab was use in those who failing initial corticosteroid and IVIG. Twelve ALPS patients were use rituximab after failure to corticosteroid.[17] Nine out of twelve patients having autoimmune thrombocytopenia responded from disease but none of the three patients treated with rituximab for autoimmune hemolytic anemia responded.

To the best of our knowledge, we cannot conclude the association between extensive JXG and ALPS as found in our patient. In the future, genomic analysis including next generation whole genome sequencing will probably explain this association.

Conclusion

We reported a case of a 6-month-old girl presented with extensive lesions of JXG and the clinical manifestation of ALPS with hepatosplenomegaly, hemolytic anemia and thrombocytopenia. ALPS was successfully treated with IVIG and Rituximab. Most

hematologic association of JXG was reported with hematologic malignancy such as juvenile myelomonocytic leukemia. No association between JXG and ALPS has ever been reported in the literature.

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