Multicentric Castleman Disease in a DOCK8 Deficient Patient with Orf Virus Infection

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Abstract

Castleman disease is a rare, heterogeneous disorder that driven by proinflammatory responses. Human herpes virus-8 has a major role in pathogenesis of multicentric Castleman disease. There is also a subgroup of cases, human herpes virus-8 negative, idiopathic multicentric Castleman disease. The role of primary immunodeficiencies in idiopathic Castleman disease are poorly described. DOCK8 deficiency is a combined primary immunodeficiency. It has a broad clinic spectrum including atopy, autoimmunity and cancer. We present a 10-year-old, DOCK8 deficient patient. He had giant lobular capillary hemangiomas on his neck, iliac and gluteal regions and multiple lymphadenopathies. Abdominal lymph node pathology revealed hyaline vascular type Castleman disease and human herpes virus-8 staining was negative. His lesions were shown to be infected with orf virus. Our case is the first case to relate idiopathic multicentric Castleman disease and DOCK8 deficiency; also, very unusual presentation of orf virus infection in humans.

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Castleman disease is a rare, heterogeneous disorder that driven by proinflammatory responses. Human herpes virus-8 has a major role in pathogenesis of multicentric Castleman disease. There is also a subgroup of cases, human herpes virus-8 negative, idiopathic multicentric Castleman disease. The role of primary immunodeficiencies in idiopathic Castleman disease are poorly described. DOCK8 deficiency is a combined primary immunodeficiency. It has a broad clinic spectrum including atopy, autoimmunity and cancer. We

present a 10-year-old, DOCK8 deficient patient. He had giant lobular capillary hemangiomas on his neck, iliac and gluteal regions and multiple lymphadenopathies. Abdominal lymph node pathology revealed hyaline vascular type Castleman disease and human herpes virus-8 staining was negative. His lesions were shown to be infected with orf virus. Our case is the first case to relate idiopathic multicentric Castleman disease and DOCK8 deficiency; also, very unusual presentation of orf virus infection in humans.

Keywords:

Idiopathic multicentric Castleman disease, DOCK8 deficiency, orf virus infection, lobular capillary hemangioma, epidermodysplasia verruciformis

Introduction

Castleman disease (CD) is a rare lymphoproliferative disorder, generally seen in adults with HIV infection, and small case series has been reported in the pediatric population [1]. Patients often have systemic symptoms due to hyperinflammation, lymphocyte polyclonality, plasma cell proliferation and fatal multiorgan dysfunction. Castleman disease is classified according to the histopathological findings, number of lymph nodes involved and presence of human herpes virus 8 (HHV-8) infection [2]. Types of CD are identified as unicentric Castleman disease (UCD), HHV-8 associated multicentric Castleman disease, HHV-8 negative/ idiopathic multicentric Castleman disease (iMCD) and polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes (POEMS)-associated MCD [2]. Two subgroups of iMCD are identified as: iMCD with thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, organomegaly (iMCD-TAFRO) and iMCD-not otherwise specified (iMCD-NOS) [2]. Several mechanisms thought to be etiological drivers such as elevated levels of human IL-6 or viral IL-6 encoded by HHV-8, other infectious or immunologic mechanisms [2]. The etiology, pathogenesis and relationship between immunodeficiencies of UCD and iMCD are poorly understood [2].

DOCK8 (dedicator of cytokinesis 8) deficiency is a rare autosomal recessive primary immunodeficiency. It is more common in populations with increased consanguineous marriages. Biallelic loss of function leads to the defect in DOCK8, which encodes guanine nucleotide exchange factor that is highly expressed in lymphocytes and regulates the actin cytoskeleton [3]. Classical findings are recurrent infections, allergic diseases including eczema and food allergy, autoimmunity and virus associated cancers [4]. Patients with DOCK8 deficiency suffer from especially cutaneous viral infections, varicella zoster, molluscum contagiosum, herpes simplex and human papillomaviruses [5]. There is no relationship shown to date that DOCK8 deficiency may cause susceptibility to orf virus infection. Orf virus is a member of*Parapoxvirus* genus, responsible for a highly contagious zoonotic viral infection that affects sheep and goats. In healthy individuals, this virus rarely causes systemic involvement and usually causes local infections, commonly orf nodules in hands. It may, however, cause more generalized illness in primary immunodeficiency patients. There are examples of orf virus-induced lobular capillary hemangiomas after thermal burns in literature. Local immunosuppression related to the burns is possible disease mechanism [13-15]. Orf infection is rarely seen in otherwise healthy individuals [6]. We present a rare case of DOCK8 deficient patient who had iMCD-NOS and orf virus infected giant lobular capillary hemangiomas.

Case Report

A 10-year-old male with giant lobular capillary hemangiomas in the ear, neck and gluteal areas, was referred to our clinic. He was the son of a Syrian refugee family, born of a consanguineous marriage. His history revealed that his lesions was first appeared as a mass in his right eyelids at four years of age. The lesions were progressive. After excision, they rapidly recurred. He had multiple lesions on his neck, iliac region and perianal areas (Figure-1A, 1B). When he admitted to our hospital, he had fever and multiple masses. He also was experiencing severe itching. The patient experienced surges of fever over 39 C once a day, for the following days. He had hepatomegaly and mild splenomegaly on physical examination. He also had multiple maculopapular lesions on his trunk; suggestive of epidermodysplasia verruciformis (Figure-1C). Broad spectrum antibiotics for possible secondary bacterial infection and acyclovir treatments were started empirically.

Human immunodeficiency virus (HIV) serology was negative. Immunohistochemical studies were negative for human herpes virus 8 (HHV8) and cytomegalovirus (CMV). Human papillomavirus (HPV) and herpes simplex virus (HSV) PCR were negative. Common etiological drivers were tested and ruled out. Additionally, we decided to test him for orf virus. Orf virus PCR samples were taken. Interestingly, the results came strongly positive for the virus (Figure-2). It was noticed that after scratching his perineal area, he would auto-inoculate the lesions by touching another body area (neck, scalp).

Our patient was anemic (hemoglobin was 8,6 gr/dl), had hypoalbuminemia (1,9 gr/dl), elevated CRP (53 mg/L) and ESR (44 mm/hour), had thrombocytosis (801 k/microL) suggesting a hyperinflammatory response. The patient's serum alkaline phosphatase (ALP) levels were high (Table 1).

Bone survey was done and revealed lytic lesions at the first metacarpal bone of the right hand. Craniocervical, abdominal, and pelvic magnetic resonance imaging (MRI) scans and thorax computed tomography (CT) were performed in order to check for additional masses. Cervical and thoracic lymphadenopaties were noted. Abdominal MRI showed multiple conglomerated lymphadenopathies in the parailiac region. T2 signal hyperintensity and contrast material enhancement were present at the medial clavicula and sternum.

An excisional biopsy was performed from the iliac lesion. Pathologic evaluation revealed lobular capillary hemangioma. The patient was given 2 mg/kg/day propranolol (p.o.), considering the effect on infantile hemangiomas.

Punch biopsy from the widespread maculopapular lesions on his trunk revealed epidermodysplasia verruciformis. Susceptibility to viral skin infections suggested an underlying combined immunodeficiency syndrome or an agent specific primary immunodeficiency. Immunological studies were remarkable for elevated serum IgE level and eosinophilia (Table 1-3). Sanger sequencing of the DOCK8 gene was done and showed homozygous mutation in NM_203447.3 c.2007+1G>T (IVS17+1G>).

Laparotomy and abdominal lymph node dissection were performed. Lymph node biopsy was compatible with the Castleman disease, hyaline vascular type including regressed/ atrophic germinal centers and lollipop appearance in some germinal centers, plasmacytosis in the interfollicular spaces, negative staining for CMV, EBV or HHV-8. Considering the multicentric lymphadenopathies, together with the histopathologic features, laboratory criteria (elevated CRP, anemia, thrombocytosis, hypoalbuminemia), clinical criteria (fever, hepatosplenomegaly) and excluding HHV-8 and HIV infection, and not detecting polyneuropathy, endocrinopathy, or monoclonal plasma cell disorder, iMCD-NOS was diagnosed. Corticosteroids and rituximab treatments were started. Due to the severity and dissemination of disease, the treatment changed to R-CHOP regimen. R-CHOP therapy was proved to be very effective, and our patient's lesions regressed dramatically after first and second cycles of chemotherapy (Figure 1D-E). Unfortunately, our patient was died because of RSV (respiratory syncytial virus) pneumonia and subsequent *P. aureginosa* sepsis after the second R-CHOP cycle.

DISCUSSION

Orf virus is a member of the *Parapoxvirus* family, and generally causes highly contagious zoonotic infections [6]. The virus causes sore mouth disease in sheep and goats [6]. In healthy individuals, especially in people who are handling sheep and goats, this virus may cause orf nodules in hands named as contagious ecthyma or contagious pustular dermatitis [6,13]. Orf virus causes skin lesions via direct contact of damaged skin with infected animals or fomites indirectly [6]. The disease course is usually self-limited, and it is not expected to cause disseminated disease, but there are very rare cases of disseminated exanthems, fever and lymphadenopathies [11]. It may, however, cause systemic disease or unexpected giant lesions in primary immunodeficiency patients [12]. Although there is susceptibility to mostly fungal infections in patients with STAT1 gain of function (GOF) defects, there has been a case of a STAT1 GOF mutation who had developed an orf virus infection [12]. Orf virus was reported to be associated with lobular capillary hemangioma in burn patients [13-15]. This may be attributed to the local immunosupression related to burn. It has been shown that the VEGF-E protein produced by orf infections causes epithelial growth in mice models [14]. It may be suggested that virally expressed VEGF-E protein may responsible for proliferative skin lessions. The

presented patient had multiple giant lobular capillary hemangiomas which are infected with orf virus.

Epidermodysplasia verruciformis is a rare, autosomal recessive skin disorder, reported a total 501 patients in literature [16]. It is characterized by high susceptibility to certain types of human papillomaviruses. Patients develops flat-topped, wart-like papular lesions similar to verrucae planae on the extremities [17]. Patients have an increased risk of developing non-melanoma skin cancers [17]. The pathogenesis is not completely understood but it is thought to be related to agent selective immunodeficiency [16]. Our patient's skin biopsy showed epidermodysplasia verruciformis. The presented patient had extensive orf virus infected giant lobular capillary hemangiomas and epidermodysplasia verruciformis lessions.

DOCK8 deficiency is a combined immunodeficiency characterized by recurrent infections, atopy, autoimmunity and cancer [3,4]. It is most commonly seen in Arabic and Turkish populations [3]. Severe cutaneous and invasive viral infections such as varicella zoster, molluscum contagiosum, HSV and HPV are seen [3,4,5]. Viral infections may be systemic or involves deep tissues [3]. DOCK8 deficiency may cause virally-driven malignencies such as HPV-related squamous cell carcinoma, EBV-related smooth muscle tumors or lymphomas [3]. This unusual occurance of orf virus infected giant lessions and epidermodysplasia verruciformis raised our suspicion towards an underlying combined or agent spesific immunodeficiency. Our patient also had eosinophilia and elevated IgE levels. Further investigations revealed DOCK8 deficiency in our patient. The presented case is first case to with DOCK8 deficiency, epidermodysplasia verruciformis and orf virus infection.

Castleman disease is a disease of unknown etiology and seen very rare in childhood [1]. The literature is mainly focused on adult population and small case series have been reported. Clinical and pathologic abnormalities are heterogeneous and overlap with a wide range of other immunologic disorders [2]. Whether autoimmune, autoinflammatory, neoplastic or infectious mechanism make the most contribution is not certain [2]. Our patient hyaline vasculary type CD and clinically had iMCD-NOS. Although the role of HHV8 in HHV8-MCD is relatively well understood, the pathogenesis of iMCD-NOS is unclear [2]. It has been showed that IL-6 overexpression may play a role in disease [18]. Interestingly, VEGF expression is also elevated in iMCD patients [19]. No certain relationship between a virus other that HIV or HHV-8 was shown to date [20]. The presented patient had multiple thoracic, cervical and abdominal lymphadenopathies. Lymph node biopsy of the conglomerated abdominal lymph nodes were performed and revealed hyaline vascular variant of multicentric Castleman disease. Our patient met the inclusion criteria for iMCD-NOS.

This patient is the first case with iMCD-NOS and DOCK8 deficiency. Drolet et al. reported a case of CD in a child with common variable immunodeficiency (CVID) [8]. Castleman disease has also been reported to occur in patients with HIV, which is an acquired T-cell deficiency. Guihot et al. documented polyfunctional effector memory HHV-8 specific CD8+ T cells in MCD and suggested that HHV-8 specific T cell responses may play a role in the pathogenesis of MCD [9]. Elevated effector memory (CD4+CCR7-CD45RA-) in our patient supports this hypothesis. Leroy et al reported a child born to consanguineous parents with proven HHV-8 associated MCD in the absence of an immunodeficiency. He suggested that MCD in childhood may be related to rare inborn errors of immunity against HHV-8 infection [10].

There are no definitive guidelines for treatment of CD and regimens vary among different institutions. The options include steroids, rituximab, anakinra, siltuximab, tocilizumab, conventional cytotoxic chemotherapy, R-CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone) and radiotherapy [2]. The presented patient responded to R-CHOP treatment very well. Our patient also had underlying DOCK8 deficiency. Hematopoietic stem cell transplantation (HSCT) is curative for DOCK8 deficiency. IFN-α treatment may also be beneficial [4]. After remission induction, we planned HSCT to our patient but unfortunatelly, our patient died because of neutropenic sepsis.

In conclusion, our case is the first case with DOCK8 deficiency, iMCD-NOS and orf virus infection. Each of these diseases are rarely seen in childhood. Our findings suggest that inborn errors of immunity may play a role in the occurrence of iMCD-NOS, and orf virus may trigger CD in the presence of an underlying immunodeficiency. Further investigations are required for understanding the immunologic basis of the disease.

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Ethical approval : Informed consent was obtained from the patient's family to publish the details and images of this case.

Conflict of Interest Disclosures: None reported.

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Table-1 . Complete blood count and biochemical features of patient

Complete blood count	At presentation	Normal range
Hemoglobin (g/dl)	**8,6**	11,5-15,5
Leukocytes (/mm3)	**27.000**	5000-13.000
Absolute lymphocyte count (/mm3)	2200	1000-5000
Absolute neutrophil count (/mm3)	**21.800**	2000-8000
Absolute eosinophil count (/mm3)	**1800**	100-1000
Thrombocytes (/mm3)	**801.000**	180.000-400.000
CRP (mg/dl)	**5,30**	0-0,8
ESR (mm/hour)	**44**	0-20
Biochemical analysis		
Albumin (g/dl)	**1,9**	3,5-5,2
ALT (U/L)	**105**	<39
AST (U/L)	**139**	<51
ALP (U/L)	**1120**	86-315
BUN (mg/dL)	7,22	5-18
Creatinine (mg/dl)	0,27	0,26-0,77
eGFR (mL/min/1.73 m^2)	>60	<60

Table-2. Microbiological features of patient

	At presentation
HIV serology	negative
HHV-8 PCR (preauricular tissue)	negative
CMV PCR (preauricular tissue)	negative
HSV PCR (preauricular tissue)	negative
HPV PCR (preauricular tissue)	negative
Orf virus PCR (preauricular tissue)	**positive**
Orf virus PCR (abdominal lymph node)	negative

Table-3 . Immunological laboratory characteristics of the patient

		At presentation	References
Immunoglobulins			
IgA (mg/dL)	319	319	70-303
IgG (mg/dL)	1340	1340	764-2134
IgM (mg/dL)	22	22	69-387
Total IgE (IU/mL)	**2601**	**2601**	1,31-165
Lymphocyte subsets (%-#)			
CD3	70 (980)	70 (980)	55-78 (1200-2600)
CD4	**28 (392)**	**28 (392)**	31-47 (650-1500)
CD8	30 (420)	30 (420)	18-35 (370-1100)
CD16+56	12 (168)	12 (168)	4-17 (100-480)
CD19	15 (210)	15 (210)	13-27 (270-860)
T lymphocyte subsets %			

		At presentation	References
CD4	**20**	**20**	29-59
Naive ($CD4^+$ $CCR7^+$ $CD45RA^+$)	**46,9**	**46,9**	57.1-84.9
Central memory ($CD4^+CCR7^+CD45RA^-$)	18,1	18,1	11.3-26.7
Effector memory ($CD4^+CCR7^-CD45RA^-$)	**24,7**	**24,7**	3.3-15.2
Temra ($CD4^+CCR7^-CD45RA^+$)	**10,1**	**10,1**	0.4-2.6
TREC ($CD4^+CD31^+CD45RA^+$)	59	59	41-81
CD8	19	19	19-29
Naive ($CD8^+CCR7^+CD45RA^+$)	**4,2**	**4,2**	28.4-80.6
Central memory ($CD4^+CCR7^+CD45RA^-$)	2,6	2,6	1-4.5
Effector memory ($CD4^+CCR7^-CD45RA^-$)	**76,5**	**76,5**	6.2-29.3
Temra ($CD4^+CCR7^-CD45RA^+$)	16,4	16,4	9.1-49.1
B lymphocyte subsets %			
CD19	34	34	
CD20	34	34	
Memory ($CD19^+CD27^+$)	1	1	18.6-46.7
Switch Memory ($CD19^+CD27^+IGD^-$)	1	1	10.9-30.4
Marginal zone ($CD19^+CD27^+IGD^+$)	0	0	5.2-20.4
Naive ($CD19^+CD27^-IGD^+$)	**97,1**	**97,1**	47.3-77
Active ($CD19^+CD38^-CD21^{lo}$)	**1,3**	**1,3**	2.3-10
Plasmablasts ($CD19^+CD38^{hi}$ IGM^-)	**0,1**	**0,1**	0.6-5.3
Transitional ($CD19^+CD38^{hi}$ IGM^-)	**0,7**	**0,7**	4.6-8.3
Lymphocyte activation test %			
CD3	48	48	45.4-74.1
CD4	13	13	-
CD25	53	53	66.9-98
CD69	77	77	70.6-83.2
$CD3^+CD25^+$	42	42	46.3-88.5
$CD3^+CD69^+$	**31**	**31**	50.3-75.6

Figure 1A: Preauricular and cervical lesions

Figure 1B: Gluteal lesions of the patient

Figure 1C: Epidermodysplasia verruciformis lesions on the trunk

Figure 1D: Preauricular and cervical lesions after one cycle of chemotherapy

Figure 1E: Significant regression of the preauricular and cervical lesions after two cycles of chemotherapy

Figure-2: Samples from lobular capillary hemangiomas was strongly positive for orf virus PCR

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