Childhood-onset Systemic Lupus Erythematosus With Trisomy X and the Increased Risk for Bone Complications: A Case Report

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Case Report

Keywords: trisomy X, systematic lupus erythematosus, corticosteroids, avascular necrosis, osteoporosis

Posted Date: December 17th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-127440/v1

Version of Record: A version of this preprint was published on February 23rd, 2021. See the published version at https://doi.org/10.1186/s12969-021-00507-3.

Abstract

Background: Childhood-onset systemic lupus erythematosus is a multi-organ inflammatory autoimmune disease mediated by immune complexes with the age of onset before 18 years. Trisomy X is the most common female chromosomal abnormality and the role of an additional X chromosome in the development of systemic lupus erythematosus is well recognized. However, the potential complications and optimal management of childhood lupus with trisomy X remain unclear. Herein, we describe a case of childhood-onset systemic lupus erythematosus associated with severe bone complications presumably secondary to trisomy X.

Case presentation: A 16-year-old Japanese girl was diagnosed with childhood-onset systemic lupus erythematosus and trisomy X. A chromosomal abnormality (47, XXX) was incidentally identified on bone marrow examination initially done to determine the cause of pancytopenia. She was initially treated with intravenous methylprednisolone pulse therapy and prescribed monthly cyclophosphamide, prednisolone, mycophenolate mofetil, and hydroxychloroquine as remission maintenance drugs. She developed generalized extremity pain that had been worsening over the course of the disease. Extremity magnetic resonance imaging performed 12 months after the treatment onset revealed multifocal avascular necrosis, and dual-energy X-ray absorptiometry revealed further deterioration and osteoporosis. High plasma levels of factor VIII were detected by additional tests for coagulation functions.

Conclusions: An additional X chromosome has been reported to be associated with factor VIII and osteoporosis. Additionally, elevated plasma levels of FVIII is the risk factors for thrombosis, which leads to the risk of avascular necrosis. Patients with systemic lupus erythematosus complicated by trisomy X are at a higher risk of avascular necrosis and osteoporosis that can also manifest in childhood systemic lupus erythematosus.

Main Text

Background

Childhood-onset systemic lupus erythematosus (cSLE) is a multi-organ inflammatory autoimmune disease mediated by immune complexes, with an age of onset before 18 years [1]. Avascular necrosis (AVN) is a well-recognized complication of systemic lupus erythematosus (SLE), but the risk of AVN is usually lower in children than in adults. The prevalence of AVN in patients with SLE ranges between 10% and 15% [2]. Conversely, the prevalence of AVN in cSLE ranges between 5.4% and 8.4% [3–5].

The importance of the X chromosome in the pathogenesis of systemic lupus erythematosus (SLE) is well recognized, but its role in the development of bone complications remains unclear. Trisomy X is the most common female chromosomal abnormality, occurring in approximately 1 in 1,000 female births; most individuals are only mildly affected or asymptomatic [6]. The risk of SLE in Klinefelter's syndrome is similar to that of normal females [7], and the prevalence of SLE in trisomy X is 2.5 times higher than in chromosomally normal females [8]. However, the studies of the clinical manifestations of SLE in

trisomy/polysomy X have been scarce, and the bone complications have not been mentioned in any of them [9–11].

Herein, we report a case of cSLE in a female patient with trisomy X that developed severe bone complications.

Case Presentation

A 16-year-old Japanese girl was referred to our hospital for fever suspected to be due to cSLE. She had a medical history of attention deficit hyperactivity disorder and was diagnosed with stomatitis at the age of 12, alopecia at the age of 14, and butterfly erythema vulgaris at the age of 15 .

At presentation, blood tests revealed pancytopenia (total white blood cell count: 3,400/mL; lymphocyte count: 958/mL; hemoglobin level: 7.9 g/dL; platelet count: 149,000/μL), low complement levels (C3: 25 mg/dL; C4: 2 mg/dL; CH50: 10 U/mL), and normal C-reactive protein levels (0.3 mg/dL). The patient tested positive for the following autoantibodies: anti-nuclear antibody titer > 1:1280, homogeneous and speckled pattern; anti-DNA antibody 520 IU/mL; anti-double stranded DNA antibody 1,010 IU/mL; anti-Smith antibody > 1:32; anti-U1 ribonucleoprotein antibody > 1:256, anti-SS-A antibody; anti-Scl-70 antibody. Tests for PR3-antineutrophil cytoplasmic antibody (ANCA), myeloperoxidase-ANCA, anti-cardiolipin antibody (IgG), lupus anticoagulant, and anticardiolipin/beta2-glycoprotein I complex antibodies were negative. Urine analysis showed proteinuria, mixed cellular casts, and red blood cells. A chromosomal abnormality (47, XXX) was incidentally identified on bone marrow examination initially done to determine the cause of pancytopenia. The patient was subsequently diagnosed as having cSLE with trisomy X. Some unusual findings that are commonly observed in the elderly were also noted. The cranial magnetic resonance imaging (MRI) showed no vascular disease, but potential signs of palladium calcification (Fig. 1a). The dual-energy X-ray absorptiometry (DEXA) performed prior to the treatment revealed low bone mineral density (lumbar spine: 0.972 g/cm^2; Z-score − 1.7).

The patient was initially treated with two courses of intravenous methylprednisolone pulse therapy (1 g/day for 3 days and maintenance therapy with prednisolone 1 mg/kg/day for 4 days) with heparinization. Thereafter, monthly cyclophosphamide treatment was added (0.5 g/m$^{2)}$ and prednisolone was tapered. Mycophenolate mofetil (MMF) and hydroxychloroquine were added for the maintenance of remission, but were discontinued secondary to their adverse effects of leukopenia and alopecia, respectively (Fig. 2). Generalized extremity pain developed early and worsened over the course of the disease. Extremity MRI performed 6 months after the treatment onset was normal. However, a second MRI performed 6 months later revealed multifocal avascular necrosis (AVN) and the increased volume of adipose tissue in the bone marrow of the spine, similar to what is observed in the elderly [12] (Fig. 1b-f).

Additional tests for coagulation defects were performed because one of the proposed mechanisms for vascular interruption in AVN is coagulation/ thrombus formation [4, 5]. Prothrombin time, activated partial prothrombin time, D-dimer levels, protein C and protein S activation, and antithrombin III activity were

normal. However, the plasma levels of factor VIII (FVIII) and VWF antigen (VWF: Ag) were extremely elevated (FVIII: 192.4%, normal range 78–165%; VWF: Ag > 201%, normal range 50–150%). These findings ruled out congenital thrombotic disorders such as protein C/S deficiency, but revealed that the potential thrombotic condition may be caused by high levels of FVIII [13] and VWF: Ag [14]. Additionally, further deterioration and osteoporosis were observed on the second DEXA (lumbar spine: 0.956 g/cm^2; Z-score − 1.8). MMF was restarted for the concerns of ongoing deterioration and rituximab was added to reduce steroid-related adverse effects, such as bone complications. Currently, she is being treated with prednisolone and MMF for SLE. However, her AVN pain has not been managed effectively.

Discussion And Conclusions

We have described a case of cSLE in a patient with trisomy X complicated by AVN and osteoporosis. In our patient the development of these complications may have been related to an additional X chromosome.

It is likely that thrombosis due to interactions between FVIII encoded by the X chromosome and VFW might have caused AVN in our patient. Elevated plasma levels of FVIII [13] and VWF: Ag [14] are the risk factors for arterial and venous thrombosis, and a recent study suggested that their levels correlate [15]. Since the gene encoding FVIII (*F8*) is located on the long arm of the X chromosome [16], the overexpression of *F8* might induce thrombosis in trisomy X patients. A case of a severe leg ulcer in XXXXY syndrome due to elevated FVIII was previously reported [17]. A case-based review of SLE in female polysomy X reported that four out of five cases developed arthritis [9], which might be attributed to AVN.

Moreover, an additional X chromosome can elevate the risk for osteoporosis. Given that Klinefelter syndrome has been associated with an increased risk of osteoporosis [7], trisomy X may similarly follow suit. In addition, some trisomy X patients can develop premature ovarian failure, which is also a risk factor for osteoporosis [6]. Our patient already had a low bone mineral density before the start of the treatment, which may have reflected the characteristics of trisomy X. Since the use of corticosteroids is a well-known predisposing factor for osteoporosis [18], extra care should be taken when corticosteroid therapy is prescribed for the trisomy X patients compared to chromosomally normal females.

In summary, it is important to consider the risk of AVN and osteoporosis in SLE patients with trisomy X more so than in chromosomally normal females, even in the case of a childhood onset.

Abbreviations

SLE
systemic lupus erythematosus
cSLE
childhood-onset systemic lupus erythematosus

AVN
avascular necrosis
ANCA
antineutrophil cytoplasmic antibody
MRI
magnetic resonance imaging
MMF
mycophenolate mofetil
FVIII
factor VIII
VWF
Ag Von Willebrand factor antigen

Declarations

Ethics approval and consent to participate: The report was conducted in adherence with the Declaration of Helsinki, and written informed consent was obtained from the patient and the patient's guardians. IRB/Ethics Committee ruled that approval was not required for this study.

Consent for publication: Written informed consent was obtained from the patient and the patient's guardians.

Availability of data and materials: Not applicable.

Competing interests: The authors declare that they have no competing interests.

Funding: Tokyo Medical and Dental University (TMDU) received unrestricted research grants for Department of Lifetime Clinical Immunology from AbbVie GK, Ayumi Pharmaceutical Corporation, Chugai Pharmaceutical Co., Ltd., CSL Behring K.K., Japan Blood Products Organization, Nippon Kayaku Co., Ltd., UCB Japan Co. Ltd., and Asahikasei Pharmaceutical Corporation.

Author's contributions: SY planned and carried out the patients' treatment and drafted the manuscript. SA, YA, and MM planned and carried out the patients' treatment and helped draft the manuscript. SM, TN, and MM contributed the critical revisions of the manuscript for important intellectual content.

All authors read and approved the final manuscript.

Acknowledgments: We would like to thank the patient and the patient's family for allowing this publication.

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Figures

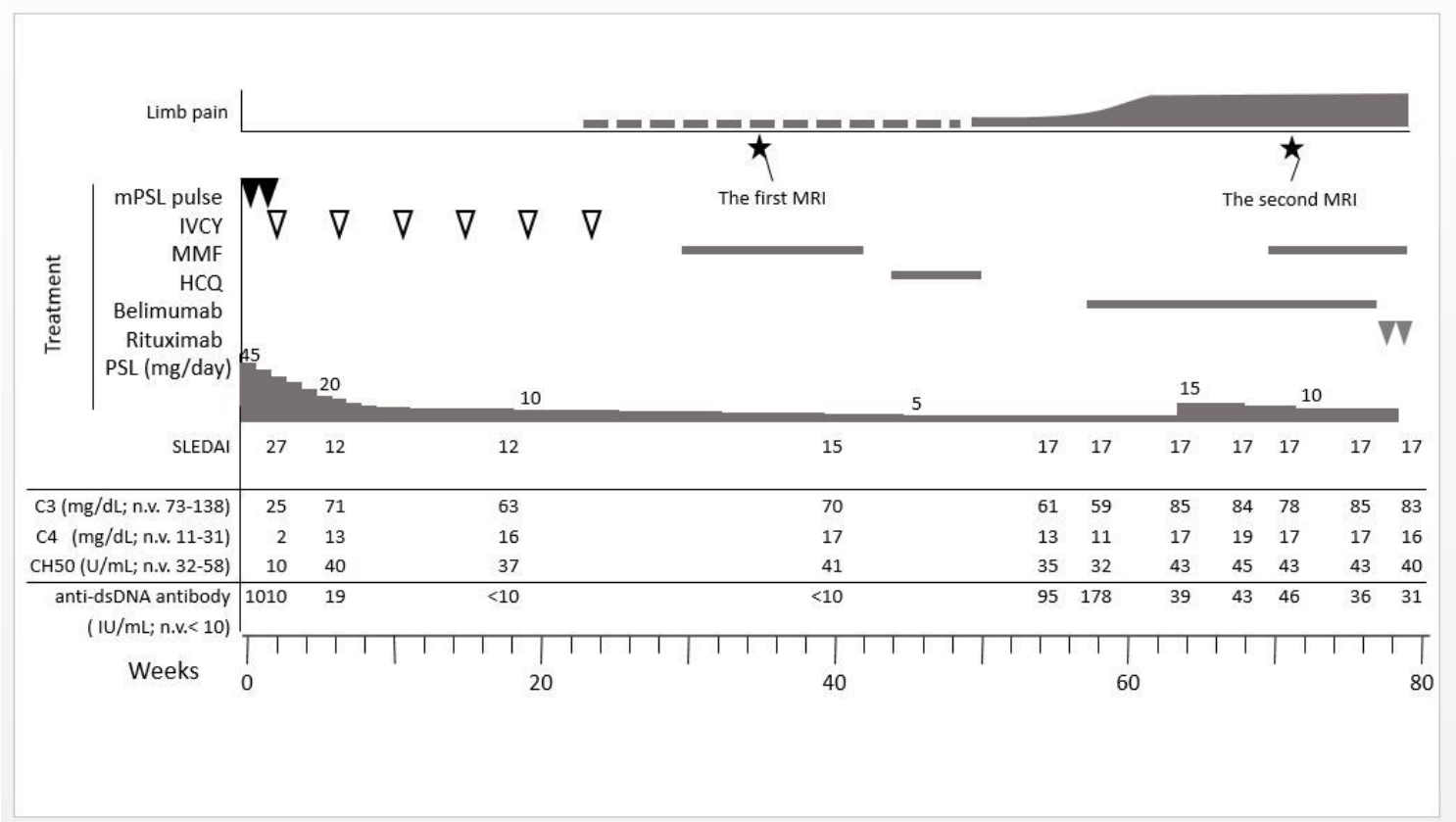

Figure 1

Clinical course of the patient. Black triangles show mPSL pulse (one course; mPSL 1 g/day for 3 days and maintenance therapy with prednisolone 1 mg/kg/day for 4 days). White triangles show monthly cyclophosphamide treatment 0.5 g/m2 (total six times). The first course of mycophenolate mofetil and hydroxychloroquine were discontinued owing to leukopenia and alopecia, respectively. From an early stage in the disease course, extremity pain had developed and worsened. HCQ, hydroxychloroquine; IVCY, intravenous cyclophosphamide; MMF, mycophenolate mofetil; mPSL, methylprednisolone; PSL, prednisolone; SLEDAI, systemic lupus erythematosus disease activity index

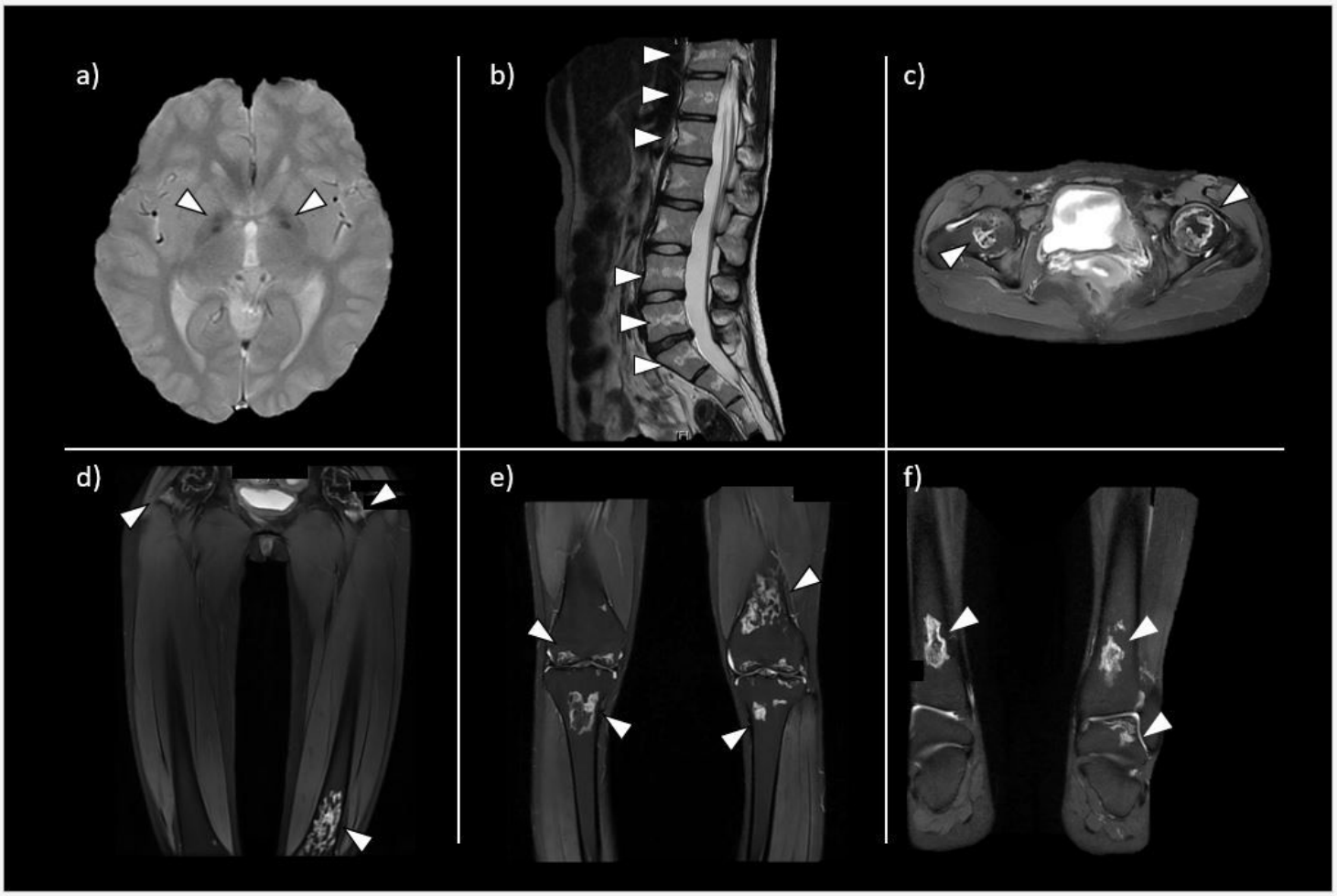

Figure 1

MRI (T2 weighted Image) findings were inconsistent with the patient's age and revealed multiple sites of AVN. Suspected calcification of the globus pallidus (a) and fatty changes in the lumbar spine (b: sagittal view), which are usually found in the elderly. AVN is seen in femoral head (c: axial view, d: coronal view); distal femur and proximal tibia (e: coronal view); distal tibia and talus (f: coronal view). AVN, avascular necrosis; MRI, magnetic resonance imaging.