



Successful treatment with cladribine of Erdheim-Chester disease with orbital and central nervous system involvement developing after treatment of Langerhans cell histiocytosis

Uspešna primena kladribina u lečenje Edhajm-Česterove bolesti sa zahvatanjem orbita i centralnog nervnog sistema nastale nakon lečenja Langerhansove histiocitoze

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Abstract

Introduction. Erdheim-Chester disease (ECD) is a rare, systemic form of non-Langerhans cell histiocytosis of the juvenile xantho-granuloma family with characteristic bilateral symmetrical long bone osteosclerosis, associated with xantho-granulomatous extraskeletal organ involvement. In ECD, central nervous system (CNS) and orbital lesions are frequent, and more than half of ECD patients carry the V600E mutation of the proto-oncogene BRAF. The synchronous or metachronous development of ECD and Langerhans cell histiocytosis (LCH) in the same patients is rare, and the possible connection between them is still obscure. Cladribine is a purine substrate analogue that is toxic to lymphocytes and monocytes with good hematoencephalic penetration. **Case report.** We presented a 23-year-old man successfully treated with cladribine due to BRAF V600E-mutation-negative ECD with bilateral orbital and CNS involvement. ECD developed metachronously, 6 years after chemotherapy for multisystem LCH with complete disease remission and remaining central diabetes insipidus. During ECD treatment, the patient received 5 single-agent chemotherapy

courses of cladribine (5 mg/m² for 5 consecutive days every 4 weeks), with a reduction in dose to 4 mg/m² in a fifth course, delayed due to severe neutropenia and thoracic dermatomal herpes zoster infection following the fourth course. Radiologic signs of systemic and CNS disease started to resolve 3 months after the end of chemotherapy, and CNS lesions completely resolved within 2 years after the treatment. After 12-year follow-up, there was no recurrence or appearance of new systemic or CNS xantho-granulomatous lesions or second malignancies. **Conclusion.** In accordance with our findings and recommendations provided by other authors, cladribine can be considered an effective alternative treatment for ECD, especially with CNS involvement and BRAF V600E-mutation-negative status, when interferon- α as the first-line therapy fails.

Key words:

erdheim-chester disease; histiocytosis, non-langerhans cells; orbital pseudotumor; central nervous system; brain stem; cerebellum; proto-oncogene proteins b-raf; cladribine; magnetic resonance imaging.

Apstrakt

Uvod. Edhajm-Česterova bolest (EČB) je redak sistemski oblik ne-Langerhansove histiocitoze iz porodice juvenilnih ksantogranuloma, koga karakteriše simetrična bilateralna osteoskleroza dugih kostiju sa ksantogranulomskom infiltracijom različitih organa. Kod EČB često su prisutne lezije centralnog nervnog sistema (CNS) i orbita, a više od polovine bolesnika sa ovom bolesti ima V600E mutaciju protoonkogena BRAF. Sinhroni ili metahroni razvoj EČB i Langerhansove histiocitoze (LH) kod

istog bolesnika je redak, a moguća veza između njih još uvek je nejasna. Kladribin je purinski analog koji deluje toksično na limfocite i monocite sa dobrom hematoencefalnom penetracijom. **Prikaz bolesnika.** Prikazali smo muškarca, starog 23 godine, koji je uspešno lečen kladribinom zbog EČB sa obostranim zahvatanjem orbita i CNS. Kod prikazanog bolesnika BRAF V600E mutacija nije bila prisutna, a EČB je nastala metahrono, šest godina nakon hemioterapijskog lečenja multisistemске LH, sa potpunom remisijom bolesti i zaostajanjem centralnog insipidnog dijabetesa. Tokom lečenja EČB, bolesnik

je dobio pet ciklusa monohemioterapije kladribinom (5 mg/m² tokom pet dana, svake 4 nedelje), uz redukciju doze na 4 mg/m² u petom odloženom ciklusu zbog izražene neutropenije i pojave herpes-zoster infekcije po okončanju četvrtog ciklusa. Rezolucija radiološki viđenih sistemskih i CNS lezija počela je nakon tri meseca, uz potpuni nestanak lezija u CNS unutar dve godine od završetka hemioterapije. Bolesnik je periodično praćen tokom 12 godina, pri čemu nije uočena pojava relapsa bolesti kao ni sekundarnog maligniteta. **Zaključak.** U odnosu na naše prikazano iskustvo i preporuke drugih autora, kladribin se

može razmatrati kao efikasna alternativna terapija za EČB, naročito kod bolesnika sa lezijama u CNS i odsustvom BRAF V600E mutacije, kada je primena interferona α kao leka prvog izbora bila neuspešna.

Ključne reči:

erdheim-chesterova bolest; histiocitoza, non-langerhans ćelije; pseudotumor orbite; centralni nervni sistem; moždano stablo; mozak, mali; proteini, protoonkogeni, b-raf; kladribin; magnetna rezonanca, snimanje.

Introduction

Erdheim-Chester disease (ECD) is a rare, non-inherited and orphan disease of unknown origin^{1,2}. It is systemic form of non-Langerhans cell histiocytosis (non-LCH) of the juvenile xanthogranuloma (JXG) family, with characteristic bilateral symmetrical long bone osteosclerosis associated with extraskeletal organ involvement in more than 50% of cases¹⁻³. Central nervous system (CNS) and orbital lesions in ECD are frequent¹⁻⁵, and more than half of ECD tested patients carry the V600E mutation of the proto-oncogene BRAF^{1,2}. ECD differs from Langerhans cell histiocytosis (LCH) clinically and in the histological, immunohistochemical and ultrastructural characteristics of the respective histiocytes^{3,6}. The synchronous or metachronous development of ECD and LCH in the same patients is rare^{1,4-7}. The choice of cladribine (2-chlorodeoxyadenosine) for ECD treatment before 2005, or the beginning of the "interferon- α era"¹, was based on its successful use in the treatment of adult and pediatric multisystem LCH^{8,9}. We reported a rare case of young man successfully treated with cladribine due to metachronous BRAF V600E-mutation-negative ECD involving the orbits and CNS after chemotherapy treated LCH, with 12-year follow-up.

Case report

A 23-year-old Caucasian male presented in August 1999 with a 6-month history of progressive severe exophthalmos and vision loss of the left eye, caused by a large orbital, retrobulbar, intraconal soft tissue mass, revealed by orbital computed tomography (CT). He also complained of occasional knees and ankles pain. He had the 6-year history of central diabetes insipidus (CDI) which had remained after chemotherapy (methotrexate, vinblastine, prednisolone) for multisystem LCH during the period 1991–1993, with complete remission of the disease. The patient underwent left transcranial upper orbitotomy with complete extirpation of the intraconal tumor, together with the optic nerve which was intimately and completely enveloped and partly infiltrated by the tumor. Histopathology showed xanthogranulomatous orbital pseudotumor. Six months later the patient noticed proptosis of the right eye. The full range of eye movements was preserved with good visual acuity. Orbital CT showed a well defined, posteromedial, retrobulbar, intraconal, orbital soft tissue mass which had displaced the right globe for-

ward and outward. In November 2000, the patient underwent debulking of the right orbital lesion. The histopathology was the same as previously reported. Despite corticosteroid treatment, the right exophthalmos worsened in the next 6 months with limitation of eye movements and decreased visual acuity. The patient also noted progressive gait incoordination and the loss of balance, legs weakness with pain, dizziness and fatigue. A contrast-enhanced head magnetic resonance imaging (MRI) in May 2001 showed enlargement of the right orbital tumor, recurrence of the left orbital tumor and multiple nodular lesions in the pons, middle cerebellar peduncles and midbrain (Figure 1). A technetium⁹⁹ (⁹⁹Tc) bone scintigraphy showed increased uptake in the proximal and distal ends of the long bones of the legs, the hands and facial bones (Figure 2). Echocardiography showed pericardial thickening with effusion and right atrial collapse. Thoracic and abdominal CT revealed mediastinal and retroperitoneal fibrosis with "hairy perirenal infiltration". Laboratory investigation disclosed an inflammatory syndrome with hypoalbuminemia. Liver biopsy was negative. Re-examination of both orbital tumor specimens confirmed xanthogranulomatosis with Touton multinucleate giant cells and lipid-laden foamy histiocytes positive for CD68, CD14 and HLA-DR, and negative for CD1a and S100 immunoreactivity, surrounded by fibrosis (Figure 3). Based on the above radiologic findings and histopathology, a diagnosis of ECD was reached. Intravenous single-agent chemotherapy by cladribine was started in August 2001, at a dose of 5 mg/m² for 5 consecutive days every 4 weeks. In total, 5 courses were given with reduction of cladribine dose to 4 mg/m² in the delayed fifth course, due to severe neutropenia and thoracic dermatomal herpes zoster infection following the fourth course. Radiologic signs of systemic and CNS disease started to resolve 3 months after the end of chemotherapy, and CNS lesions completely resolved within 2 years of treatment. The progression of cerebellar symptoms was arrested but there was no regression of neurological deficit. The orbital lesions partially regressed and scarred. CDI was controlled with desmopressin. Yearly follow-ups showed no recurrences or appearances of new systemic or CNS xanthogranulomatous lesions (Figure 4) or second malignancies 12 years after cladribine treatment. The patient is still alive. Subsequently, the BRAF V600E-mutation status in both paraffin-embedded orbital tumor specimens was determined by allele-specific real-time polymerase chain reaction (detection limit less than 1%), and presence of the V600E mutation were not detected.

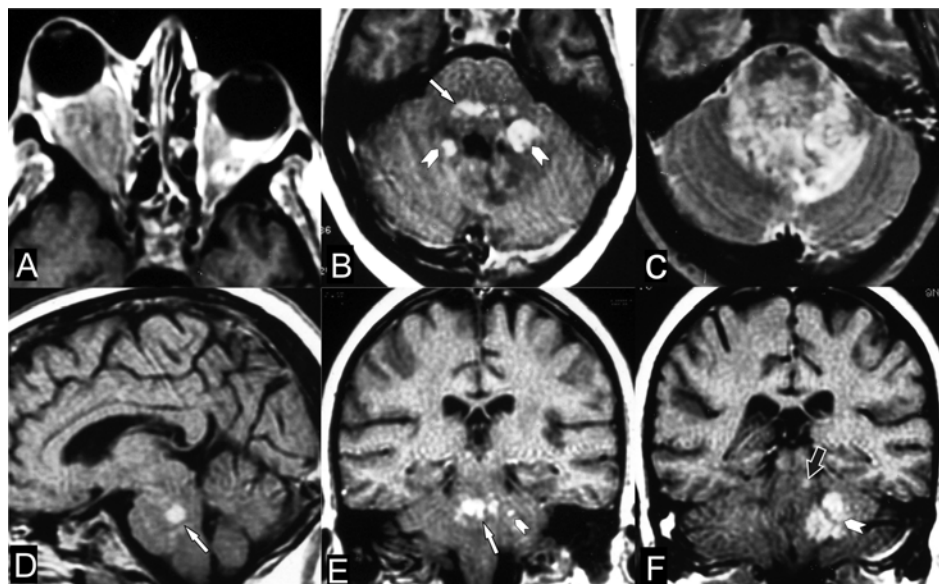


Fig. 1– Post-contrast axial T1-weighted magnetic resonance imaging (MRI) demonstrates enhancing (A) right orbital, retrobulbar massive infiltration with prominent exophthalmos and recurrence of the left retrobulbar mass, as well as (B) nodular enhancing lesions in the pontine tegmentum (white arrow) and the middle cerebellar peduncles (white arrowheads) with perifocal edema. Axial T2-weighted MRI (C) shows bright asymmetric hyperintense signal in the pontine tegmentum and the middle cerebellar peduncles predominantly on the left side. Post-contrast sagittal (D) and coronal (E, F) T1-weighted MRI demonstrates nodular enhancing lesions in the pontine tegmentum (white arrows), left middle cerebellar peduncle (white arrowheads) and ipsilateral midbrain tegmentum (black arrow).

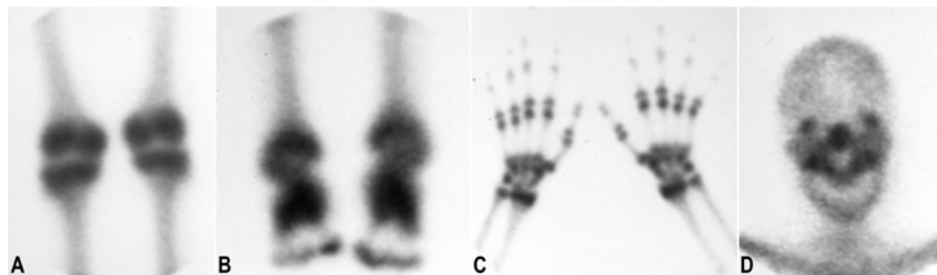


Fig. 2 – ^{99m}Tc bone scintigraphy shows symmetric and abnormally increased technetium uptake in (A) the distal ends of the femurs and the proximal ends of the tibiae, (B) the distal ends of the tibiae and the tarsal bones bilaterally, (C) the distal ends of the ulnae and the radii as well as bilaterally in some of the carpal bones, the proximal and distal ends of the metacarpal bones and the proximal ends of the proximal phalanges, and in (D) the facial bones.

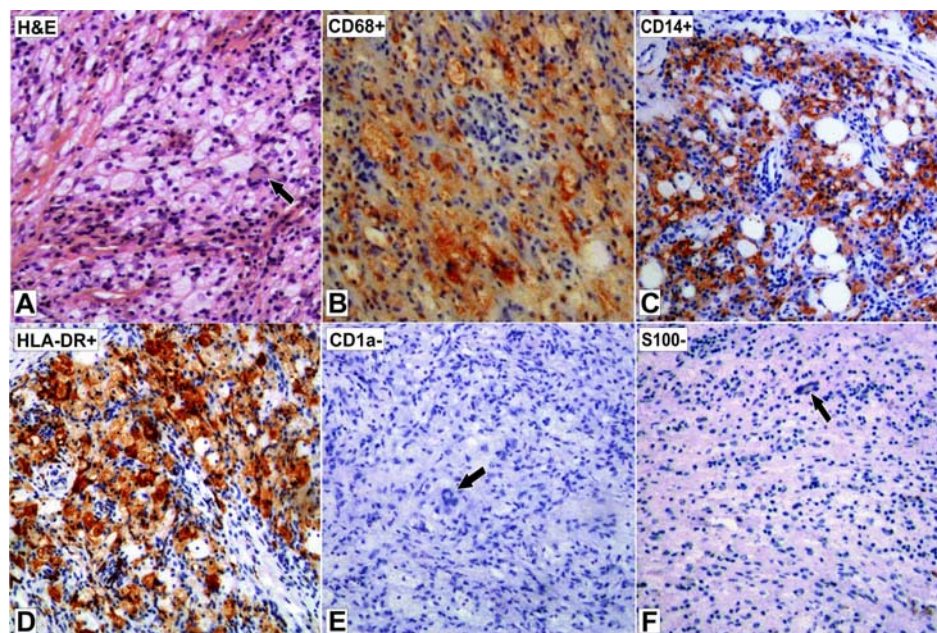


Fig. 3 – Photomicrographs of the right orbital retrobulbar surgical specimen shows (A) clusters of foamy histiocytes intermixed with mature lymphocytes and individual Touton multinucleate giant cell (arrow) nested in fibrosis (hematoxylin and eosin staining). Immunohistochemistry of the same specimen shows foamy histiocytes positive for (B) CD68, (C) CD14 and (D) HLA-DR, and negative for (E) CD1a and (F) S100 immunoreactivity (immunohistochemical staining with DAB as a chromogen contrasted with hematoxylin). Touton multinucleate giant cell (arrow) is also negative for (E) CD1a and (F) S100 immunoreactivity. The original magnification of all images (A-F) is $\times 100$.

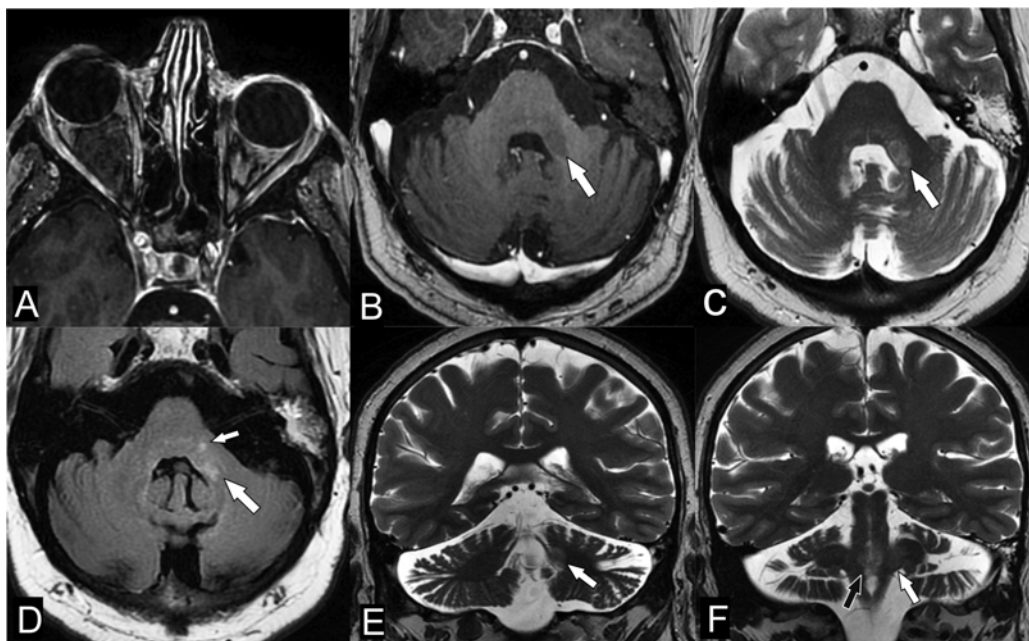


Fig. 4 – Post-contrast axial T1-weighted magnetic resonance imaging (MRI) after 12 years follow-up demonstrates residual, no enhancing (A) right orbital, retrobulbar, intraconal scar tissue with significantly less pronounced exophthalmos and the absence of left retrobulbar infiltration, as well as (B) a hypointense gliotic scar in the left middle cerebellar peduncle (white arrow). Axial T2-weighted (C), T2-weighted fluid attenuated inversion recovery (D) and coronal T2-weighted (E, F) MRI demonstrates a slightly hyperintense gliotic scar in the left middle cerebellar peduncle (white arrows) and in the pontine tegmentum (black arrow).

Discussion

ECD is a multisystemic disease whose extent and distribution determines the clinical course^{1,2}. Widely accepted diagnostic criteria of ECD are the following¹⁻⁶: typical histological findings – xanthogranulomatosis with CD68-positive and CD1a-negative immunostaining; characteristic skeletal abnormalities – symmetric and abnormally intense labeling of the distal ends of the long bones of the legs revealed by⁹⁹Tc bone scintigraphy. Our patient fulfilled both criteria. Painful skeletal lesions in our patient were accompanied by mediastinal, retroperitoneal, pericardial, orbital and CNS involvement.

CNS involvement in ECD is a strong prognostic factor and an independent predictor of death^{1,10}. Infiltrative nodular lesions in the brainstem, cerebellum and especially in the middle cerebellar peduncles have frequently been reported⁴⁻⁶, as was the case in our patient, resulting in cerebellar and pyramidal syndromes with severe handicaps of ECD patients^{1,5}. The typical MRI features of infiltrative ECD CNS lesions are bright hyperintensity on T2-weighted sequence and intense homogeneous gadolinium enhancement on T1-weighted sequence without mass effect^{4,5}, as we observed in our patient, with prolonged gadolinium retention of the lesions even after several days⁵. Other described forms of CNS involvement in ECD were meningioma-like lesions, pituitary stalk infiltration and intracranial periarterial infiltrations^{4,5}. Surgical resection is only reasonable in ECD patients with circumscribed intracranial meningioma-like lesions and resulting focal neurological deficits. As an initial diagnostic method, intracranial biopsy procedures should be performed only when diagnosis of the systemic disease is not possible¹¹. Orbital involvement in

ECD is often bilateral and intraconal^{1,2,4}, and frequently associated with osteosclerosis of the facial bones^{2,4} as in the case of our patient. Surgical debulking of orbital lesion is required as in our case, when retrobulbar infiltration is massive and refractory to conventional therapy¹.

ECD mainly affects middle-aged adults with male predominance^{1,2}. In this case, the patient was a young man who developed ECD following chemotherapy treated LCH with residual CDI. Reportedly, 11% of ECD patients have associated LCH^{1,5}. Several theories have been proposed to explain synchronous coexistence or metachronous development of ECD and LCH^{2,6,7}, but still without conclusive answers. Theoretically, an abnormality in the common CD34+ progenitor cell could be responsible for both diseases, depending on changes in the cellular cytokine microenvironment at different points in time. Additionally, metachronous ECD following chemotherapy treated LCH could represent an evolution, maturation or conversion of LCH to non-LCH (ECD), with differentiation switch of the respective histiocytes due to a change in patient's immune response induced by therapeutic interventions⁷.

ECD is a systemic form of non-LCH of the JXG family, composed of histiocytic cells exhibiting monocyte/macrophage differentiation^{3,6}, and with increased monocyte activation in the peripheral blood¹². Cladribine is an antimetabolite that is toxic to lymphocytes and monocytes, with good hematoencephalic penetration^{8,13}. Tissue histiocytes and circulating monocytes have common progenitor cell origin³. These facts, together with the reports that described encouraging response to cladribine in adult and pediatric patient with LCH^{8,9}, made the use of cladribine in ECD with CNS involvement a rational therapeutic choice. This was the

main reason to choose cladribine as a first-line therapy for our patient at the time of his treatment (August 2001 – January 2002), before beginning of the “IFN- α era”¹. Despite residual neurological deficit, we considered the cladribine treatment to have been successful, providing good and long-lasting remission to our patient 12 years after ending the treatment. Myra et al.¹² also reported a significant recovery and maintained clinical improvement in a patient with ECD with orbital involvement 2 years following treatment with cladribine.

As for adverse effects, cladribine may be associated with dose-dependent myelosuppression, and neurological toxicity². Also, cladribine is a powerfully immunosuppressive purine substrate analogue, its incorporation into DNA may be mutagenic with the risk of secondary malignancies⁸. Our patient had a severe neutropenia and thoracic dermatomal herpes zoster infection which occurred after the penultimate course of cladribine and resulted in a dose reduction and delay of the last cladribine course, with no secondary malignancies during the 12-year follow-up. It is possible that an alternative 3-day dosing schedule (5–6.5 mg/m²/day for 3 days, every 3–4 weeks)⁹ would be less myelotoxic with the same efficiency as the one used.

Currently, IFN- α is the most extensively studied agent in the treatment of ECD and serves as the first line of treat-

ment^{1,2,14}. Furthermore, treatment with IFN- α was identified as an independent predictor of survival¹⁰. Since more than half of ECD tested patients carry BRAF V600E mutation, targeted therapy with vemurafenib, an inhibitor of V600E-mutated BRAF, represents promising treatment option in multisystemic and refractory cases of BRAF V600E-mutation-associated ECD, particularly if life-threatening^{1,14}. Cladribine is advocated as an alternative treatment for ECD^{2,14} and may be beneficial for treating CNS ECD lesions that are not responsive to IFN- α ¹, especially in BRAF V600E-mutation-negative ECD patients, which is in accordance with our experience in this case.

Conclusion

Erdheim-Chester disease is a rare and orphan multisystemic disease whose management and treatment is complex. Central nervous system involvement in Erdheim-Chester disease is associated with severe morbidity and mortality. Since there is still no definitive cure, the goals of Erdheim-Chester disease treatment should be prolonging life and maximizing its quality. Presented case of Erdheim-Chester disease with orbital and central nervous system involvement, with good and long-lasting response to cladribine just confirms this.

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Received on September 15, 2014.

Revised on January 9, 2015.

Accepted on January 12, 2015

Online First June, 2015.