Case Report / Приказ болесника

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A rare complication in a child undergoing chemotherapy for Hodgkin lymphoma – multiple cerebral venous sinus thrombosis

Ретка компликација у детета током хемотерапије Хочкиновог лимфома – вишеструке тромбоze церебралних венских синуса

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Received: December 7, 2020
Revised: November 17, 2021
Accepted: December 4, 2021
Online First: December 8, 2021
DOI: https://doi.org/10.2298/SARH201207102K

*Accepted papers are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the Serbian Archives of Medicine. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.

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When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

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Summary
Introduction Risk factors for thrombotic events in patients receiving treatment for Hodgkin lymphoma are not well known. Administration of some cytostatic medication, especially via central venous catheter, corticosteroids and hyperlipidemia can present some of them. Case outline A case of a 15-year-old boy that had been newly diagnosed with Hodgkin lymphoma is presented here. Chemotherapy according to vincristine, etoposide, prednisone, and doxorubicin (OEPa) protocol was introduced a month before headache and vomiting occurred, so subsequently, brain-computer tomography (CT) was performed, and revealed laminar subdural pseudo hemorrhage in the right occipital region. After performing magnet resonance imaging (MRI) venous thrombosis of the posterior part of superior sagittal sinus, right transverses and sigmoid sinus were presented. Low-molecular-weight heparin (LMWH) and anti-edematous therapy was immediately initiated. Two weeks later the patient resumed the second cycle of chemotherapy combined with LMWH, as the previous symptoms of intracranial hypertension resolved. Two years after MRI showed almost complete resolution of finding. The boy was in good clinical condition. Conclusion Although administration of oral corticosteroids could be rarely a risk factor per se for cerebral sinus venous thrombosis in HL patients, it remains important treatment option. Adequate and prompt diagnostics and therapy are mandatory in cases of wide intracranial venous thrombosis as prevention of possible intracranial hypertension and even fatal outcome.

Keywords: Hodgkin lymphoma; chemotherapy; cerebral venous sinus thrombosis

INTRODUCTION

French clinician Ribes has published the first case of thrombosis of the sagittal sinus in a man who had suffered from altered conciseness and epilepsy, nearly two centuries ago [1]. Recently many facts considering pathogenesis, cause and risk factors occurred, and novel diagnostic procedures and therapy options evolved. Risk factors associated with cerebral sinus venous thrombosis (CSVT) are proved to be inherited or acquired. The most frequently associated risk factor is congenital thrombophilia. If acquired, risk factors are numerous, like brain trauma [2], infections of the central nervous system [3] or local infections [4], nephrotic

САЖЕТАК
Увод Фактори ризика настанка тромбозе болесника леченih од Хочкиновог лимфома (ХЛ) nisu do kraja razjasnjeni. Primena nekih цитостатика, нарочито преко централне венске линије, кортикостерои и хиперлипидемија могу бити неки од њих.

Приказ болесника У раду је приказан случај дечака, 15-годишњака, коме је постављена дијагноза ХЛ. Према терапијском протоколу винкристина, етопозида, преднизона и доксорубицина (ОЕПА) ординирана је хемотерапија, месец дана пре појаве главобоље и повраћања, па је компјутеризована томографија мозга урађена, и показала је постојање танковног пseудосубдуралног хематома у пределу десног окципиталног режња. Након урађене магнетне резонансе мозга показао је готово полне нормализацију стања. Дечак је био у добром клиничком стању.

Закључак Иако примена оралних кортикостероида може укључити други циклус хемотерапије у комбинацији са ХЛ, пошто су се знаци интракранијалне хипертензије повукли. Наклон две године МР налаз мозга показао је готово потпуну нормализацију стања. Дечак је био у добром клиничком стању.

Кључне речи: Хочкинов лимфом; хемотерапија; тромбоза венског церебралног синуса

DOI: https://doi.org/10.2298/SARH201207102K Copyright © Serbian Medical Society
syndrome [5] cranial tumors [6], hematological conditions [7], medicaments and cranial surgery, pregnancy and puerperium [8].

Although we found a case of the girl that had cerebral venous thrombosis (CVT) in non-Hodgkin lymphoma [9] while reviewing the literature we couldn’t find a description of Hodgkin lymphoma (HL) in children complicated specific by CSVT [10]. This case could be the first one published.

CASE REPORT

A 15-year-old boy was diagnosed with HL, *sclerosis nodularis CS IIIA*, two months before admission at Clinic for Neurosurgery. The chemotherapy according to vincristine, etoposide, prednisone, and doxorubicin (OEPA) protocol was introduced and he tolerated it well. Dose were for vincristine 1.5 mg/m$^2$ IV on day 1, 8 and 15, etoposide 125 mg/m$^2$ IV from 1. to 5. day, prednisone 60 mg/m$^2$, per os (PO) 1-15 day, and doxorubicin 40 mg/m$^2$ intravenous (IV), 1. and 15. day [11]. After the second cycle of the therapy severe headache, and vomiting occurred. Immediately, brain computer tomography (CT) was done (fig 1.) and a radiologist described laminar occipital subdural bleeding, so the patient was sent for the neurosurgical examination from the local medical center.

After admission, conservative therapy was introduced 20% Mannitol 60ml/12h as anti-edematous therapy and paracetamol a 500 mg when needed. Also, diazepam a 5mg every evening. His initial white blood cell count was 0.5 x 10$^9$/L, neutrophils 0.04 x 10$^9$/L lymphocytes 0.37 x 10$^9$/L, monocytes 0.02 x 10$^9$/L, and thrombocytes 158 10$^9$/l. After that brain magnetic resonance imaging (MRI) and angio-MRI were performed and revealed (fig 2), not a hemorrhage but thrombosis of the superior sagittal sinus (SSS) (Fig 2A), right transverse (RTS) (Fig 2B) and sigmoid venous sinus (RSS) (Fig 2C). Foci of filling defect in the lumen of the sinuses with “empty-delta” sign on T2-weighted images appeared but no signs of cerebral ischemia (fig 2 A).

His coagulation status appeared to be normal, international normalized ratio (INR) 1.3, prothrombin time (PT) 26s, partial thromboplastin time (PTT) 75% were also in the normal
range. Another MRI was performed 10 days after and no changes in finding were observed. Coagulation profile on the next day was as follows: PT 15s seconds, activated PTT 40.7 seconds, d-dimer 2.1 ug/mL, fibrinogen 241 mg/dL, cholesterol 140 mg/dL, and triglyceride (TG) 122 mg/dL. The eye exam has shown a normal finding of the fundus. Low-molecular-weight heparin (LMWH), Fraxiparin was also administered subcutaneously in a dose of 2 x 0.6 ml per day. Few episodes of headaches appeared again during the disease, and the patient was treated 3 to 4 days with Mannitol 60ml/12h, paracetamol, and antiseizure prevention as diazepam a 5mg in the evening.

Patient wasn’t genetically tested. There weren’t any data about malignancies or blood diseases in family history. The levels of antithrombin, protein C and S were normal, as well as the reaction of factor V to activated protein C.

After three weeks the patient was discharged from hospital in good clinical status and LMWH were administrated during the following six months. His INR values were between 2.3 and 3.1. After LMWH oral anticoagulant therapy rivaroxaban (Xarelto) 15 mg a day was administered for a few months. After that antiplatelet therapy, acetylsalicylic acid (Cardiopirin) 100mg was administrated up to the present day. A follow-up examination of brain MRI after 6 and 12 months revealed the partial resolution of thrombosis. There were no clinical symptoms or signs related to thrombosis. Two years after, control brain MRI (Fig 3) showed a complete resolution of the previous finding – minor residua of thrombosis. The boy was in good clinical condition.

This case report was approved by the institutional ethics committee, and written consent was obtained from the patient’s parent/guardian for the publication of this case report and any accompanying images.

**DISCUSSION**

Hodgkin's lymphoma is a lymphoid neoplasm, usually presented with specific histopathologic and clinic characteristics. Neurologic complications of HL are due to the disease itself or can be iatrogenic. Headache is the most common clinical manifestation in 89%,
followed by focal deficit and epilepsy in one half and one-third of the cases respectively [12]. The first-choice diagnostic procedures are MRI and MR venography, while LMWH is a cornerstone of the treatment worldwide [12].

Why did the patient develop the CVST? Administration of L-asparaginase, dyslipidemia and high body mass index in a child with acute lymphoblast leukemia (ALL) can cause the SSST. Hyperlipidemia is known to be one of the risk factors for cerebral venous sinus thrombosis, and L-asparaginase, a major component in effective ALL treatment, is highly associated with temporal hypertriglyceridemia in the pediatric population [13]. Corticosteroids alone can induce the activity of lipoprotein lipase, which may prevent a rise in TG on corticosteroid therapy [14]. On the other hand, some experimental studies [15, 16] showed that levels of clotting factors and fibrinogen are rapidly increased by glucocorticoids. In the population-based case-control study of Johannesdottir et al. patients on corticosteroids had an increased risk of venous thromboembolism (VTE) and the effect was strongest for new users of systemic glucocorticoids [17]. Also, an interesting finding was that oral glucocorticoids were associated with a higher risk than the injectable form. They affect tissue factor-mediated leukocyte procoagulant activity and inhibit platelet aggregation in a later phase of treatment, and in general, may not be the only reason for hypercoagulability in our patient. Chemotherapy for HL may lead to cerebral infarction on the base of embolism due to cardiomyopathy. Anthracycline may induce cardiomyopathy [18].

Our patient was not treated with either of the above-mentioned cytostatic, but according to OEPA protocol, and a large cohort of 66329 cancer patients with any malignancy presented a finding that chemotherapy-treated patients had double increased risk of VTE compared to those who had not [19]. In our case report patient received also oral prednisone 60 mg/m² for 15 days, and that could be the reason for developing CVST, besides chemotherapy. He had a normal body mass index, and there were no laboratory findings of dyslipidemia, and his coagulation status appeared to be normal. Also, we haven’t performed genetically tests [20] for congenital thrombophilia and that is significant shortcoming of the study.

Administration of the cytostatic via a central venous catheter (CVC) is also a significant risk factor for development VTE. David et al. observed that 36% of NHL patients with catheters, regardless of therapy, experienced VTE events [21]. Our institutional practice has been to administer OEPA via peripheral IV unless there was another indication for central
access. In a particular case, the boy received therapy via a peripheral vein. Anyway, CVC related thrombosis are not located in the brain High grade NHL is associated with the highest incidence rate of VTE (8.3 %), followed by low-grade NHL and HL, 6.3 %, and 4.7 % respectively [22].

Risk factors for thrombotic events in patients receiving treatment for HL are not well known. The largest and most comprehensive analysis of thrombotic events in HL patients is a study of Borchmann et al. A total of 193 thrombotic events occurred for an incidence of 3.3%; among 5,773 HL patients and advanced-stage patients were at higher risk for VTE. Prophylactic anticoagulant treatment is not warranted even for higher stage HL patients, as long as they remain mobile or are without a history of the previous thrombosis [23]. The most frequent location of thrombosis in HL patients are upper and lower extremity and lungs [24]. The most common location sites for CVT, in the general population, are transverse sinus 86%, superior sagittal sinus 62%, straight sinus 18%, cortical veins 17%, jugular veins 12%, the vein of Galen and internal brain veins 11% [25].

Starting from the middle of the 20th century, when CVT was considered a fatal illness, up to the MRI era, many series have shown a steady decrease in mortality. In recent studies reported mortality rates in the acute phase were 4.3% and 3.4% in evolution after 30 days [26]. Factors of bad prognosis are male sex, age over 37, altered conscious, deep CVT, papilledema, and Glasgow Coma Scale < 9 [27].

Adequate and prompt diagnostics and therapy are mandatory in cases of wide intracranial venous thrombosis as prevention of possible intracranial hypertension and even fatal outcome. Although administration of oral corticosteroids, could be rarely a risk factor per se for cerebral sinus venous thrombosis in HL patients, it remains important treatment option.

**Conflict of interest:** None declared.
REFERENCES


**Figure 1.** Initial brain computed tomography of the 15-year-old boy with sudden headache and vomiting; A: axial scan shows right occipital hyperdense area; B: enlarged axial scan presenting altered signal in the area of the right transverse sinus
Figure 2. Brain MRI; A: axial T2W tomogram shows “empty-delta” sign; B and C: axial FLAIR tomograms show thrombosis right transverse sinus (RTS) and right sigmoid sinus (RSS); D: MR angiogram presents thrombosis of the superior sagittal sinus, RTS, and RSS
Figure 3. A: T2W axial tomogram presents recanalization of the superior sagittal sinus (SSS) (no delta sign); B: T1W postcontrast axial tomogram presents recanalization of the SSS; C: 3D magnetic resonance venography sinus recanalization