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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

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

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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 was performed, and reviled laminar subdural pseudo-hemorrhage in the right occipital region. After performing magnetic 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 later, MRI showed an almost complete resolution of the 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 Hodgkin lymphoma patients, it remains an important treatment option. Adequate and prompt diagnostics and therapy are mandatory in cases of wide intracranial venous thrombosis as the prevention of possible intracranial hypertension and even fatal outcome.
Keywords: Hodgkin lymphoma; chemotherapy; cerebral venous sinus thrombosis

INTRODUCTION

A French clinician Ribes [1] 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. Recently, many facts considering pathogenesis, cause, and risk factors emerged, and novel diagnostic procedures and therapy options evolved. Risk factors associated with cerebral sinus venous thrombosis 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 syndrome [5], cranial tumors [6], hematological conditions [7], medicaments and cranial surgery, pregnancy and puerperium [8].

Although we found a case of a girl that had cerebral venous thrombosis (CVT) in non-Hodgkin lymphoma [9], while reviewing the literature we could not find a description of Hodgkin lymphoma (HL) in children complicated specifically by cerebral sinus venous thrombosis [10]. This case report 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 to the Clinic for Neurosurgery. The chemotherapy according to vincristine, etoposide, prednisone, and doxorubicin (OEPA) protocol was introduced and the patient tolerated it well. The dose for vincristine was 1.5 mg/m^2 IV on day 1, 8, and 15; for etoposide 125 mg/m^2 IV days 1–5; for prednisone 60 mg/m^2, *per os* days 1–15; and for doxorubicin 40 mg/m^2 IV, days 1 and 15 [11]. After the second cycle of the therapy, severe headache and vomiting occurred. Immediately, brain computer tomography was done (Figure 1) and a radiologist described laminar occipital subdural bleeding, so the patient was referred from the local medical center to a neurosurgical examination.

After admission, conservative therapy was introduced – 20% mannitol 60 ml/12h as anti-edematous therapy, and 500 mg of paracetamol when needed, as well as 5 mg of diazepam every evening. His initial white blood cell count was 0.5 × 10^9/L, neutrophils 0.04 × 10^9/L, lymphocytes 0.37 × 10^9/L, monocytes 0.02 × 10^9/L, and thrombocytes 158 × 10^9/L. After this, brain

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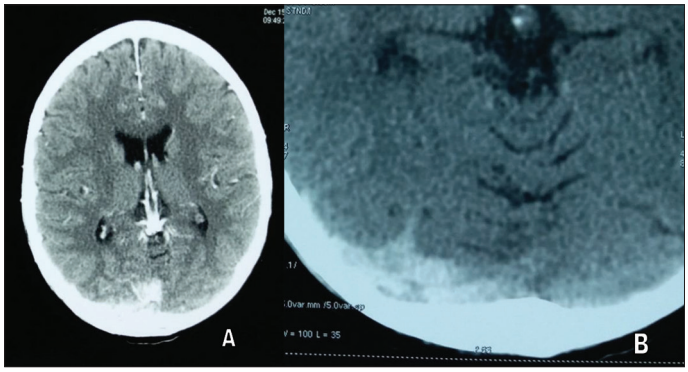

Figure 1. Initial computed tomography of the brain of a 15-year-old boy with sudden headache and vomiting; A: axial scan shows right occipital hyperdense area; B: enlarged axial scan presenting altered signal in the area of the right transverse sinus

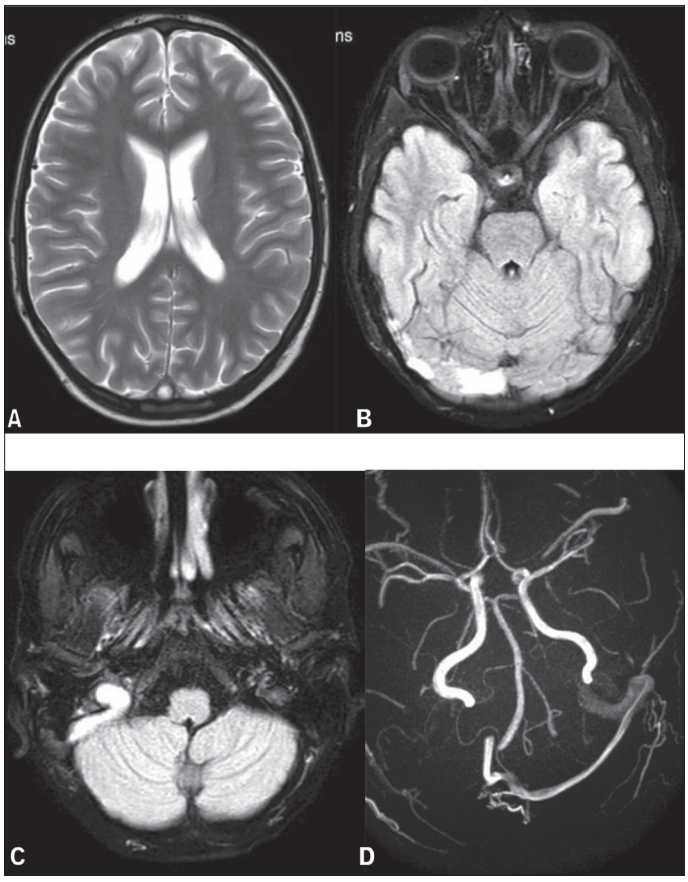

Figure 2. Brain MRI; A: axial T2W tomogram shows the "empty-delta" sign; B and C: axial FLAIR tomograms show thrombosis right transverse sinus (RTS) and right sigmoid sinus (RSS); D: MR angiogram presents thrombosis of the superior sagittal sinus, RTS, and RSS

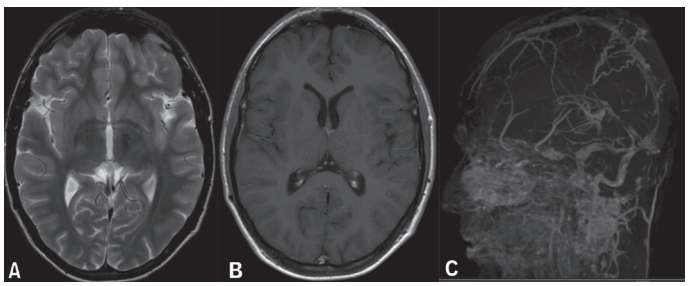

Figure 3. A: T2W axial tomogram presents recanalization of the superior sagittal sinus (SSS) (no delta sign); B: T1W postcontrast axial tomogram presents recanalization of the SSS; C: 3D magnetic resonance venography sinus recanalization

magnetic resonance imaging (MRI) and angio-MRI were performed and revealed not a hemorrhage but thrombosis of the superior sagittal sinus (SSS) (Figure 2A), right transverse (RTS), (Figure 2B), and sigmoid venous sinus (RSS) (Figure 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 (Figure 2A).

The patient's coagulation status appeared to be normal, international normalized ratio (INR) of 1.3, prothrombin time (PT) of 26 seconds, partial thromboplastin time (PTT) of 75% were also in the normal range. Another MRI was performed 10 days later and no changes in findings were observed. Coagulation profile on the next day was as follows: PT 15 seconds, activated PTT 40.7 seconds, D-dimer 2.1 μg/mL, fibrinogen 241 mg/dL, cholesterol 140 mg/dL, and triglycerides (TG) 122 mg/dL. The eye exam showed a normal finding of the fundus. Low-molecular-weight heparin (LMWH), Fraxiparine® (Glaxo Wellcome Production, Notre Dame de Bondeville, France) was also administered subcutaneously in a dose of 2 × 0.6 ml per day. Several episodes of headache appeared again during the disease, and the patient was treated three to four days with mannitol 60 ml/12h, paracetamol, and 5mg of diazepam in the evening as antiseizure prevention.

The patient was not genetically tested. There were not any data about malignancies or blood diseases in family history. The levels of antithrombin, proteins 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 condition and LMWH were administrated during the following six months. His INR values were 2.3–3.1. After LMWH, oral anticoagulant therapy rivaroxaban (Xarelto, Bayer AG, Leverkusen, Germany) 15 mg a day was administered for a few months. After that, antiplatelet therapy, acetylsalicylic acid (Cardiopirin, G.L. Pharma GmbH, Lannach, Austria) 100mg has been administrated up to the present day. A follow-up examination of brain MRI after six and 12 months revealed the partial resolution of thrombosis. There were no clinical symptoms or signs related to thrombosis. Two years later, control brain MRI (Figure 3) showed a complete resolution of the previous finding – minor residua of thrombosis. The boy was in a 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

HL 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 SSS thrombosis. 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 showed that levels of clotting factors and fibrinogen are rapidly increased by glucocorticoids [15, 16]. In the population-based case–control study by Johannesdottir et al. [17], patients on corticosteroids had an increased risk of venous thromboembolism (VTE) and the effect was the strongest for new users of systemic glucocorticoids. 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 basis of embolism due to cardiomyopathy. Anthracycline may induce cardiomyopathy [18].

Our patient was not treated with either of the abovementioned cytostatic, but according to the OEPA protocol, and a large cohort of 66,329 cancer patients with any malignancy, chemotherapy-treated patients had double increased risk of VTE compared to those who had not received chemotherapy [19]. In our case report, the patient also received oral prednisone 60 mg/m^2 for 15 days, and that could be the reason for developing CVST in addition to 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 did not perform genetic tests for congenital thrombophilia and that is a significant shortcoming of the report [20].

Administration of the cytostatic via a central venous catheter (CVC) is also a significant risk factor for developing VTE. David et al. [21] observed that 36% of NHL patients with catheters, regardless of therapy, experienced VTE events. Our institutional practice has been to administer OEPA via peripheral IV unless there was another indication for central access. In this particular case, the boy received therapy via a peripheral vein. Nonetheless, CVC-related thrombosis are not located in the brain. High-grade non-Hodgkin lymphoma is associated with the highest incidence rate of VTE (8.3%), followed by low-grade non-Hodgkin lymphoma 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 by Borchmann et al [23]. A total of 193 thrombotic events occurred for an incidence of 3.3%; 5773 HL patients and advanced-stage patients were at a 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 a previous thrombosis [23]. The most frequent location of thrombosis in HL patients are upper and lower extremities 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 rate in the acute phase was 4.3%, and 3.4% in evolution after 30 days [26]. Factors of poor prognosis are male sex, age over 37 years, altered consciousness, deep CVT, papilledema, and Glasgow Coma Scale score < 9 [27].

Adequate and prompt diagnostics and therapy are mandatory in cases of wide intracranial venous thrombosis as a 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 an important treatment option.

Conflict of interest: None declared.

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Ретка компликација код детета током хемотерапије Хоџкиновог лимфома – вишеструке тромбозе церебралних венских синуса

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САЖЕТАК

Увод Фактори ризика настанка тромбозе болесника лечених од Хоџкиновог лимфома нису до краја разјашњени. Примена неких цитостатика, нарочито преко централне венске линије, кортикостероди и хиперлипидемија могу бити неки од њих.

Приказ болесника У раду је приказан случај дечака, 15-годишњака, коме је постављена дијагноза Хоџкиновог лимфома. Према терапијском протоколу винкристина, етопозида, преднизона и доксирубицина (ОЕПА) ординирана је хемиотерапија месец дана пре појаве главобоље и повраћања, па је урађена компјутеризована томографија мозга и показала је постојање танког псеудосубдуралног хематома у пределу десног окципиталног режња. Након урађене магнетне резонанце мозга заправо је откривена тромбоза горњег сагиталног синуса, десног транзверзалног и сигмоидног венског синуса. Ординирани су нискомолекуларни хепарин и антиедематозна терапија. После две недеље болеснику је укључен други циклус хемиотерапије у комбинацији са нискомолекуларним хепарином, пошто су се знаци интракранијалне хипертензије повукли. После две године налаз магнетне резонанце мозга показао је готово потпуну нормализацију стања. Дечак је био у добром клиничком стању.

Закључак Иако примена оралних кортикостероида може повремено бити фактор ризика за развој церебралних тромбоза венских синуса код болесника са Хоџкиновим лимфомом, они остају као незаобилазан вид третмана. Адекватна и брза дијагноза и терапија су обавезне у случајевима са раширеном венском тромбозом, а ради превенције интракранијалне хипертензије и последичног смртног исхода.

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