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CANCER-ASSOCIATED STROKE IN A PATIENT WITH TESTICULAR CANCER – CASE REPORT

MOŽDANI UDAR UDRUŽEN SA KARCINOMOM KOD BOLESNIKA SA KARCINOMOM TESTISA – PRIKAZ SLUČAJA

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Summary

Introduction. Cerebral venous thrombosis is a rare cerebrovascular disease that affects about 5 in 1 million people each year and accounts for 0.5% of all strokes. There is significant overlap of many risk factors for cerebral venous thrombosis and venous thromboembolism: cancer, obesity, genetic thrombophilia, trauma, infection, and prior neurosurgery. Testicular cancer is a malignant tumor found in testicular cells and it is generally called testicular germ cell tumor. This case report puts emphasis on the importance of recognizing cerebral venous thrombosis as one of the cancer-associated symptoms that can help set the appropriate diagnosis, which, however, is not very common for this type of disease. **Case report.** A 58-year-old patient has been examined many times due to recurrent strokes. Lumbar puncture, computed tomography scan, magnetic resonance imaging, magnetic resonance angiography, magnetic resonance venography, immuno-serology and electroencephalography have been performed. Apart from the vascular changes in the brain blood vessels, the cause of the stroke was not clear. Furthermore, the patient was examined by a hematologist and an urologist. Laboratory testing showed increased levels of alpha fetoprotein and beta-human chorionic gonadotropin, however, no tumor was found in the suspected testis. Eventually, the patient underwent retroperitoneal lymph mass percutaneous core biopsy procedure and was diagnosed with non-seminoma germ cell tumor – Yolk sac tumor. **Conclusion.** Patients with cerebral venous thrombosis require multidisciplinary approach for the appropriate diagnosis.

Key words: Testicular Neoplasms; Stroke; Venous Thrombosis; Intracranial Thrombosis; Diagnosis; Biomarkers, Tumor; Biopsy; Risk Factors

Sažetak

Uvod. Cerebralna venska tromboza predstavlja retko cerebrovaskularno oboljenje koje pogađa pet od jednog miliona ljudi i čini 0,5% svih moždanih udara. Postoji značajno preklapanje različitih faktora rizika za cerebralnu vensku trombozu i venski tromboembolizam: rak, gojaznost, trombofilija, trauma, infekcija, prethodna neurohirurška intervencija. Rak testisa predstavlja maligni tumor ćelija testisa kod muškaraca i uopšteno se naziva tumor zametnih ćelija testisa. Ovaj prikaz slučaja naglašava značaj prepoznavanja cerebralne venske tromboze kao mogućeg pratećeg simptoma maligne bolesti koji može pomoći u postavljanju odgovarajuće dijagnoze. **Prikaz slučaja.** Pedesetosmogodišnji bolesnik je više puta pregledan zbog ponavljajućih moždanih udara. Načinjena je lumbalna punkcija kao i kompjuterizovana tomografija, magnetna rezonanca, magnetno-rezonantna angiografija i venografija, imunoserologija i elektroencefalografija. Osim patoloških promena u krvnim sudovima mozga, uzrok moždanog udara nije utvrđen ovim ispitivanjima. Nadalje, ovog bolesnika su pregledali hematolog i urolog. Laboratorijski nalazi pokazali su povišene vrednosti alfa fetoproteina i beta humanog horio gonadotropina, ali nije postavljana dijagnoza tumora u sumnjivom testisu. Naposletku je bolesniku načinjena perkutana iglena biopsija retroperitonelanih limfnih čvorova abdomena čime je postavljena dijagnoza tumora zametnih ćelija testisa − tumor žumančane kese. **Zaključak.** Bolesnici sa cerebralnom venskom trombozom zahtevaju multidisciplinarni pristup radi postavljanja pravovremene tačne dijagnoze.

Ključne reči: tumori testisa; moždani udar; venska tromboza; intrakranijalna tromboza; dijagnoza; tumorski biomarkeri; biopsija; faktori rizika

Introduction

Cerebral venous thrombosis (CVT) is a rare cerebrovascular disease that affects about 5 in 1 million people each year and accounts for 0.5% of all strokes [1]. It was previously thought to be most commonly caused by infections (mastoiditis, otitis, meningitis) that affect the superior sagittal sinus and often result in focal neurologic deficits, seizures, coma and death. CVT mainly affects children and young adults and is an important cause of stroke in the younger population [2]. There is significant overlap of many risk factors for CVT and the ones for venous thromboembolism (VTE): cancer, obesity, genetic thrombophilia, trauma, infection, and prior neurosurgery [3].

Testicular cancer (TC) is a malignant tumor found in testicular cells of men and it is generally called testicular germ cell tumor (TGCT) [4]. TC is

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Abbreviations

CVT – cerebral venous thrombosis
CT – computed tomography scan
VTE – venous thromboembolism
TC – testicular cancer
TGCT – testicular germ cell tumor
MRI – magnetic resonance imaging
MRA – magnetic resonance angiography
MRV – magnetic resonance venography
EEG – electroencephalography
LDH – lactate dehydrogenase
AFP – alpha fetoprotein
β- h*CG* – beta-human chorionic gonadotropin
CNS – central nervous system

a rare disease, accounting for 1 to 2% of all male neoplasms. However, TC is the most common malignancy among 20 to 34-year-old men [5, 6]. There are two main types of TGTC -seminomas and non-seminomas. Seminomas usually develop later in life, in the fourth and the fifth decade, whereas non-seminomas occur among younger men between their second and third decade of life, and they are more aggressive [7]. In Europe, TGCT is the most common cancer in young men with over 18,000 new cases diagnosed annually. Further estimations predict that there will be a 25% increase in cases by 2025 across the industrialised countries [8].

This case report puts emphasis on the importance of recognizing CVT as one of the cancer-associated symptoms that can help set the appropriate diagnosis, which, however, is not very common for this type of disease.

Case report

A 58-year-old patient was first admitted to a hospital in June 2019 due to cryptogenic stroke followed with right-sided weakness. He had controlled hypertension and no family diseases in his medical history. He was treated with intravenous thrombolytic therapy and was diagnosed with left parasagittal intracerebral hematoma. Notwithstanding the therapy, the patient continued to suffer from neurological disorders in a form of headaches and right sided facial and body paresthesia. The control computed tomography (CT) scan showed partial thrombosis of the sagittal sinus, while the magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) performed in the hospital failed to confirm the sagittal sinus thrombosis. All of the additional medical tests, including immuno-serology and electroencephalography (EEG), were referent. After been discharged from the hospital, he was readmitted only two weeks later due to right-side impairment and persistent headache.

New MRI/MRA/MRV, as well as lumbar puncture, were performed during his hospitalization. MR showed two small subacute ischemic spots in the cingulate gyrus region of the same side with suspected thrombosis of left parietal veins. The lumbar puncture showed pleocytosis and hyperproteinorrachia, but infectious inflammatory diseases were excluded by an infectious disease specialist as the virology panel was negative. Furthermore, the patient was examined under the suspicion of paraneoplastic syndrome. The full-body CT scan showed retroperitoneal and inguinal lymphadenopathy up to 25 mm, but the consulted hematology specialist excluded any hematology diseases based on values of beta-2 microglobulin, lactate dehydrogenase (LDH), peripheral blood smear and the extended immunoserology tests. The patient was discharged with prescribed oral anticoagulant therapy due to thrombosis. He was admitted to the same hospital a month later for additional diagnostics that included lumbar puncture and MRI/MRA/MRV of the brain. The lumbar puncture was referent and the MRI did not show any significant brain pathology except superior sagittal sinus thrombosis. Gastroscopy showed no evidence of tumor. During the same hospitalization, the patient experienced psycho-organic syndrome and was treated with a psychiatric drug. From then on, the patient occasionally experienced epileptic attacks. He was hospitalized in June 2020 for the fifth time due to right-sided plegia and altered state of consciousness. The CT scan showed multiple both-sided frontal hemorrhages and the MRI/MRA/MRV showed new-onset hemorrhages in the temporal region, impassible anterior communicating artery and superior sagittal sinus thrombosis. In order to expose the underlying cause of neurological symptoms, further examinations were performed in the direction of vasculitis. The hemostasis, additional immuno-serology and tumor marker results were all referent as well as the granulomatous lung disease. Without the exposed underlying cause, the patient's condition was worsening and some of the diagnostic procedures such as MRI/MRV/MRA were redone. The MRI/MRA/MRV showed the early seen radiological findings that were described as chronic. The patient was admitted to the hospital six months later due to the same neurological symptom as before, and CT scan, MRI and EEG were performed. The CT scan showed hypodense spot that may correspond to ischemia in the left parietal region. The MRI showed impairment in comparison to the earlier MRI from April 2021 in the form of edema of the parietal and partially frontal region accompanied by vein thrombosis. The EEG showed no evidence of epilepsy. Onconeural antibodies (Amphiphysin, CV2, PNMa2, Ri, Zo, Hu, Recoverin, SOX1, Titin) were negative. The patient was admitted for further examination only two months later. This time, the examination included re-consultation with a hematologist and consultation with a urologist. The ultrasound of the scrotum showed smaller size of the left testicle, estimated at about 20 mm of the long diameter, inhomogeneous. Alpha fetoprotein (AFP) and beta-human chorionic gonadotropin (β- h*CG*) were increased (AFP 1576.4 β- hCG 11.6 lactate dehydrogenase referent). Histopathology results of the left testis showed no evidence of tumor. The CT scan performed in September 2021 showed enlargement

of the retroperitoneal mass of 50x40x52 mm and 45x34x54 mm this time. After he was admitted to the same hospital in September 2021, the patient underwent retroperitoneal lymph mass percutaneous core biopsy procedure. The histopathology findings showed non-seminoma germ cell tumor (NSGCT) – Yolk sac tumor (original HP number 6816/21 – CD117+, Desmin -, S100-, HMB45-, MDM2-, AFP+/-, Glypican 3+, CKMNF116+.) The patient was finally referred to the Oncology Institute of Vojvodina for further treatment.

Discussion

The prevalence of CVT in patients with malignancy is believed to be approximately 0.3% [9, 10]. Malignancy-related thromboses of the dural sinus or cerebral veins are thought to represent roughly 7.4% of all CVT cases, with cancer increasing risk for CVT roughly 5-fold [11]. Hematologic malignancies appear to be implicated more so than solid organ malignancies; however, the underlying reasons for this are not completely understood [12]. The pathogenesis of CVT in the setting of malignancy is not well defined [13]. Several potential mechanisms have been proposed including direct tumor compression, tumor invasion, and the hypercoagulable state of malignancy [10, 14, 15]. In the absence of tumor compression or invasion, malignancy-related prothrombotic states are thought to drive development of venous thromboembolism (VTE) via a variety of mechanisms including a tumor's ability to increase the expression of tissue factor, cancer procoagulant, and inflammatory cytokines as well as to downregulate the expression of thrombomodulin and the protein C system [16].

Data from a Finland study that has investigated 589 CVT patients without prior malignancy showed that 2.3% of all patients experienced new cancer diagnosis during the follow up; the risk of a new cancer diagnosis was higher in men than in women in the same age group <50, but with no sex difference in older patients. No particular cancer type was predominant. Four of the new cancer diagnoses occurred within a year after the CVT, 3 in men and 1 in women (all in different organs) [17].

Studies of hospitalized cancer patients have noted a VTE incidence of 0.6% to 7.8%, with higher rates reported among patients receiving chemotherapy and the ones with pancreatic, ovary, kidney, lung, stomach and brain tumors [18, 19].

As a vast majority of common CVP causes was excluded in this patient's case (thrombophilia, inflammation, infection, etc.) we continued with further research towards malignancies. Knowing that hematologic malignancies appear to be implicated more than solid organ malignancies, hematological disease was excluded. We need to note that the patient's left testis was smaller but histopathology findings did not show any testicular malignancy as an underlying cause of CVT. A later CT scan showed enlargement of retroperitoneal lymph mass that appeared to be metastatic lesion of testicular cancer. Srikanthan et al. have shown that a large (maximum axial diameter more than 5cm) retroperitoneal lymphadenopathy (RPLN) is a strong risk factor for VTE in TGCT [20]. In addition to positive nodal disease factors, a metastatic disease, high LDH and age over 30 can also affect VTE in patients with testicular cancer [21]. Our patient did not have any clinical signs of peripheral venosus thromboembolism. On the contrary, he had signs of central thromboembolism even though he had not received any platinum-based therapy. Platinum based chemotherapy is associated with treatment-related toxicities like thromboembolic events [22].

Most patients with germ cell tumors are young without many comorbidities, which should lower their VTE risk. However, the cancer itself and cisplatin markedly increase their VTE risk. In a study that included 179 patients with germ cell cancer, 8.4% developed thromboembolic complications [23]. In another study that included 153 patients undergoing cisplatin-based chemotherapy, 26 (17%) developed VTE. As opposed to VTE, literature data did not show many patients with testicular cancer who experienced CVT without peripheral thrombosis [24]. Furthermore, processing this patient, we wanted to exclude angiitis of the central nervous system (CNS), where CNS remains a poorly understood form of vascular inflammatory disease. Primary angiitis of the CNS (PACNS), a disease once considered extremely rare, has recently been reported more frequently. Secondary vasculitis of the CNS can occur with a variety of other conditions and diseases; each requiring a different diagnostic and therapeutic approach [25]. Only a few data in literature describe relation between primary CNS angiitis and testicular cancer. Our patient's MRI/MRA/MRV showed minor bleeding and impassable anterior communicating artery in June 2020, so he underwent additional searches in order to exclude secondary vasculitis. He did not undergo stereotaxic biopsy of the described spots in order to elucidate the presence of primary angiitis of the CNS.

Data from the literature suggest that patients with testicular carcinoma are more likely to develop limbic, brainstem and hypothalamic anti-Ma2 antibody positive encephalitis than CVT. Our patient did not have any of the above diagnosis on his CT/MR scans or the lumbar puncture findings.

Even there are well known CVT and VTP risk factors, the most common acquired CVT risk factors are oral contraceptive use and pregnancy, which explains why CVT is 3 times more likely to occur in young and middle-aged women [3]. However, other causes must not be neglected.

Conclusion

Patients with cerebral venous thrombosis require multidisciplinary approach for the appropriate diagnosis. In every day clinical practice, cancers must not be omitted as one of the possible causes of cerebral venous thrombosis.

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