Archives of Psychiatry and Psychotherapy, 2020; 1: 49–55

DOI: 10.12740/APP/110017

Violent behaviour as a result of delirium superimposed on dementia in the course of primary central nervous system lymphoma

Aleksander Turek, Karolina Machalska, Valentyn Bezshapkin, Adrian Andrzej Chrobak, Marcin Siwek, Dominika Dudek

Summary

Primary central nervous system lymphoma is a rare neoplasm, exceptionally responsible for developing a frontal lobe syndrome. A 71-years-old patient with primary central nervous system lymphoma had undergone frontotemporal craniotomy for tumor removal. Month later, showing syncopies, disorientation and slurred speech, he was transported to Department of Internal Medicine. Neuroimaging revealed numerous tuberous changes in frontal and parietal lobes and frontotemporal area. During hospitalization, patient exhibited inadequate affect, jocular behaviour, was disoriented in the place and time, and unaware of his health state. He took repeated, uncritical attempts to jump out the window and started to exhibit persecutory delusions and hallucinations. Immediate brain radiotherapy was recommended by the oncology specialists. However, the patient did not consent to the recommended method of treatment due to his lack of recollection of the tumor or the craniotomy. The patient was forcibly transferred to Department of Psychiatry. After five weeks of treatment, the patient's condition improved significantly, and the patient regained memory of the tumor.

primary central nervous system lymphoma, amnesia, frontal lobe syndrome, consent capacity, delirium

INTRODUCTION

Primary central nervous system lymphomas (PCNSL) are extra-nodal, malignant, Non-Hodgkin type lymphomas. Their primary location is limited to brain structures, meninges, eyeballs and spinal cord [1]. The incidence is relatively low (4.7 cases per 1,000,000 people in a year) and PCNSL are most frequently diagnosed in people older than 60 years and in patients with immunodeficiencies (e.g. during the course of HIV infection or during immunosuppressive therapy) [2]. Nowadays, the neoplasm is being diagnosed more frequently in immunocompetent people between 5th and 7th decade of life, what is explained by more advanced neuroimaging techniques [3]. The most common symptoms of primary brain lymphoma are cognitive dysfunctions, psychomotor retardation, personality changes, disorientation [4]. Increase of intracranial pressure was observed in about half of the patients. The cerebellar signs (e.g. atax-

Aleksander Turek[1], Karolina Machalska[1], Valentyn Bezshapkin[1], Adrian Andrzej Chrobak[2], Marcin Siwek[3], Dominika Dudek[2]:
[1]Students' Scientific Association of Affective Disorders, Jagiellonian University Medical College, Krakow, Poland; [2]Department of Adult Psychiatry, Jagiellonian University Medical College, Krakow, Poland; [3]Department of Affective Disorders, Jagiellonian University Medical College, Krakow, Poland
Correspondence address: alekt94@gmail.com

ia, gait dysfunction, nystagmus) or brainstem signs (e.g. dysphagia, bradycardia, respiratory dysfunction, coma) were observed in 10-40% of patients [5]. The psychiatric symptoms are frequent and unspecific among patients with neoplasms of central nervous system (CNS).

In the meta-analysis of 148 cases of brain tumours accompanied by psychiatric symptoms, the authors observed no connections between specific psychiatric symptoms and localization or histological type of the tumour. The psychiatric symptoms were observed in 90% of the cases with frontal lobe lesions, supporting the practice of deepened psychiatric examination in patients with frontal lobe tumours [6]. Acute psychosis, affective disorders, memory deficits, anorexia without dysmorphophobia, drug resistance, the occurrence of new symptoms atypical to the main illness or the recurrence of old controlled symptoms should be treated as indications for exclusion of the neoplastic process during diagnostic process [7].

Median life expectancy after PCNSL diagnosis in immunocompetent patients is 14 months and 5 year survival rate reaches 31.2% of patients. The most important prognostic factors are immunodeficiencies (congenital or in the course of immunosuppressive treatment), age (above 60 years old) and the overall state of the patient. The base for diagnosis is brain imaging – however, due to the fact that PCNSL can mimic other brain tumours, the definitive conclusion can only be settled with biopsy results. The term "secondary CNS lymphoma" refers to CNS involvement in patients with systemic lymphoma. In the course of systemic lymphoma, the risk of CNS involvement estimates from 2-24% and depends on the type of lymphoma [8]. Exclusion of systemic lymphoma is obligatory in diagnostic process of PCNSL. The article describes the case of a patient with PCNSL diagnosis, who was in need of whole brain radiotherapy. Neoplastic progress resulted in dementia, frontal lobe syndrome, and delirium, and manifested in risky behaviours, that is numerous attempts to jump out of the window. As a result of amnesia, the patient could not give informed consent to optimal treatment.

Case study

A 71-years-old male patient presented acute progressive memory and speech impairment accompanied by disorientation. He was unemployed, with secondary education and had worked as a teacher and office worker. His son died due to a chronic disease 6 months before the manifestation of the patient's symptoms. In the diagnostic process, malignant neoplasm of the left frontal lobe of the brain with multiple tumors in the left fronto-temporal and right occipital areas was detected. The patient had never been treated psychiatrically before. The neuropsychological examination at the admission had found inappropriate social behaviour, poor social judgement, numerous speech deficits, and dysfunctions of writing, planning, reaction inhibition, and visuospatial functions.

The patient underwent left frontotemporal craniotomy with the removal of the left frontal lobe tumor with the meningeal decompression. The procedure was performed without complications and the patient was discharged home after a week's stay at the hospital. Histopathological examination found the neoplastic change to be a diffuse large B-cell lymphoma (DLBCL) with high proliferative index. According to the patient's wife, his behaviour had changed since the procedure. She reported that her husband's memory, speech and overall orientation was gradually deteriorating. The rapid deterioration occurred about a week after discharge from the hospital, when the patient, without warning, left the house and wandered about 2 km from where he lived – he was found later by the police, whom he could not say the reason for leaving the house or his then whereabouts.

About 2 weeks after the discharge, the patient was transported from home by a medical emergency team to a hospital emergency department due to limited contact and speech impairment. During the neurological examination at the emergency department, the patient was conscious and able to perform simple commands, yet the logical speech and contact with the patient was limited, the speech was unclear. The patient was defending himself with his limbs. Neuroimaging of the CT was conducted and found supratentorial single, diffused, tumour-like changes poorly enhanced by radio-

contrast, surrounded by grade 1 edema: in frontal lobes to 17mm in diameter, in right parietal lobe to 18mm. In left frontoparietal area changes to 32mm in diameter with decay in central area to 32mm, surrounded by grade 2-3 edema. The ventrical system dislocated 4mm to the right side, not expanded, left ventricle pressed slightly. Shallowing of left hemisphere sulci was observed, probably as a result of an edema. State after frontotemporal craniotomy was observed. This image was compared to CT performed 2 days after last surgery, which revealed only extensive, hipodensive edema-like change on the left hemisphere. The CT images and apparent state after left frontotemporal craniotomy indicated an active neoplastic process with micrometastasis in the CNS. The consulted specialist neurosurgeon declared the surgical intervention unnecessary. Due to the emergence of new symptoms, fainting and collapse, the patient was admitted to the Department of Internal Medicine and Geriatrics. After five days' stay at the ward without further complications, in the early morning hours, the medical personnel found the patient on the windowsill of the open window, clutching in one hand a religious image and in the other a blanket. The patient admitted he wanted to jump, but after the personnel's intervention he resigned, leaving the windowsill and lying in bed. He later declared during the conversation with the doctor on duty that it was too high, he had thought it over and decided not to jump. Direct restraints were applied in the form of belts for four limbs and a psychiatric consultation was held on the same day. Despite limited verbal contact due to slurred and unclear speech, the patient was accurately oriented in space, but was unable to give the current year, made a mistake in his birth date, was unaware of the cancer or the purpose of his hospital stay. Patient presented an inadequate affect, elevated mood, and jocular behaviour with derailment. During the conversation with his wife, the patient was unable to recall him standing on the windowsill and strongly denied suicidal thoughts. The patient spoke pejoratively about the hospital staff: "the morons work here". According to other patients from the ward, the patient was agitated and presented inadequate behaviour the night before the incident. The consulting psychiatrist did not, however, declare the patient's behaviour as a deliberate suicide attempt (contrary to the ward's personnel) and assessed that the probable cause of the patient's state was psychomotor disinhibition, caused by the changes in frontal lobes. The patient was diagnosed with mental disorders caused by brain damage. Psychiatrist recommended haloperidol 7mg/day, diazepam 12mg/day and continuation of direct restraint for 4 limbs. Over the following days, the patient's state did not change. When left out of restraining belts, the patient uncritically kept trying to go out the window. Two other psychiatric consultations were conducted and yielded similar conclusions as the previous one – the patient's behaviour was explained with neurological damage. Haematological consultation confirmed no tumour spreading out of the central nervous system. As a result of group oncological consultation, in order to potentially cure the disease and to reduce current psychiatric symptoms, the planned optimal treatment was a radical whole brain radiotherapy. The patient was not aware of the lymphoma in the brain, he also did not recall the tumor removal surgery – he claimed that his last procedure was inguinal hernia surgery about 7 years ago. Arguing the lack of disease, the patient did not agree to a radical radiotherapy. According to the radiology specialists, performing effective radiotherapy without the consent and cooperation of the patient was not possible, and in the current situation the therapy could even result in the death of the patient. It was decided not to start the radiotherapy until the patient gave his consent. The patient during previous treatment on Internal Medicine and Geriatrics Ward was given dexamethasone iv.8mg/day, haloperidol 6mg/day, potassium chloride 1.5g/day, nadroparine sc. 0.3ml (2850 IU)/day, in the last days diazepam 12mg/day. After a week's treatment at the ward, the court decided o transport the patient in an obligatory mode to the Department of Psychiatry in University Hospital in Cracow.

At the admission to the psychiatric ward, the patient was disoriented in space and time, in illogical and hindered contact, psychomotorically in norm. The patient presented jocular behaviour and was unaware of the reason for admission to the hospital or his disease. In addition to previously persistent symptoms, persecutory delusions and visual hallucinations were di-

agnosed, which according to the patient began to appear several days before the admission. The obligatory hospitalization was considered as justified due to the following persistent symptoms: disorientation, disorganised and violent behaviour (including the attempts to jump out the window), persecutory delusions and visual hallucinations. The patient strictly denied suicidal and homicidal thoughts and tendencies. Testing for HIV infection, hepatitis B and C showed a negative result. Pharmacotherapy in a form of: nadroparine sc. 0.3ml/day, pantoprazole 20mg/day, potassium chloride 1.5g/day, estazolam 2mg/day, dexamethasone 8mg/day, haloperidol 6mg/day was applied. Over the first week of stay at the psychiatric ward the patient complained about insomnia, constantly woke up during the night and talked to himself – zopiclone 7.5mg was administered ad hoc. The patient was keen to talk to the medical personnel and other patients, but was disoriented in time and confused about the current year and day of the month. He did not recall the recent periods of agitation or the windowsill incident, interpreted by the local personnel as a suicide attempt. When asked about his then whereabouts, he answered: "where the insane are". The patient did not understand the reasons for his admission to hospital and reasoned the intervention of third parties, probably neighbors, was to blame – he felt that someone wants his death and he did not feel safe at the ward. He uncritically demanded that he leave the hospital, explaining that he needed to buy a tombstone for his son. Due to lack of memory of the brain surgery and cancer, the patient consistently and strictly opposed the beginning of radiotherapy. Over the time of the treatment, the dose of haloperidol was gradually increased.

On the second week of the treatment, improvement in orientation in time and space was observed. Communication with the patient improved, he logically and calmly answered questions. On the third week the patient accurately completed MMSE and clock test. The patient stopped complaining about his insomnia and started to complain about the boring ward. The patient oriented completely, started to remember past events connected with surgery and CNS neoplastic disease. After being presented with the possible negative side effects of radiotherapy, the patient consented to the treatment, saying: "I didn't agree, and then I regretted, as I did not know, what's going on". In the following week, the patient, after the consultation in the radiotherapy clinic, was qualified for treatment with cerebral irradiation. The patient himself assessed his condition as good and used his permits spending time with his wife. At the beginning of the next week of treatment, in the evening hours, the patient complained of insomnia and, holding his chest, declared that the nurse had given him poison. ECG examination at the time of the incident and the next day showed no pathology, then lorazepam 1 mg was administered. The next day the patient initially denied the accusations of poisoning, later he admitted that "he could make a joke like that". The dose of haloperidol was increased to 12.5mg/day.

At the end of fifth week of treatment, the patient was declared to be comprehensively oriented and aware of his disease so as to make an informed decision about treatment. The patient presented aligned mood and drive and denied having suicidal thoughts and hallucinations, no delusional content was noticed in his statements. He was transferred to palliative ward diagnosed with dementia with an episode of delirium in the course of CNS lymphoma and isolated brain lymphoma as a secondary disease.

DISCUSSION

The patient was repeatedly diagnosed in a relatively short time with differing diagnoses, including primary lymphoma of the central nervous system, mental disorder caused by organic brain damage, dementia and delirium. The most probable cause of the presented symptoms would be the growing brain tumor seen in neuroimaging and related treatment. During first period of treatment at the Department of Internal Medicine, the radical disinhibition presented by the patient was attributed to the organic damage of frontal lobes. However, at the Department of Adult Psychiatry, delirium was considered to be the possible explanation for the patient's risky behaviour. In the context of the presented patient, all possible explanations seem to be overlapping in time, which could have hindered an unambiguous diagnosis.

According to the patient's wife and the preoperative neuropsychological consultation, the man exhibited dementia symptoms, such as memory or speech disorders, disordered visuospatial functions and disorientation in the closest environment. By that time, the patient had already presented the symptoms of dysfunctions of the frontal lobes – he was overly and inappropriately friendly, as well as exhibited signs of executive functions disorders in the domains of planning and inhibition. Cognitive disorders are not rare during the course of cancer of CNS. Half of the families of the patients with brain glioma have retrospectively recognized some signs of neurocognitive deficits in the patients, with 30% also finding changes in their personalities before the diagnosis [9]. Deficits in at least one of the neuropsychologically tested domains (memory, executive functions and attention) were found in 90% of the patients with tumors in frontal or temporal areas before the beginning of treatment [10]. Mass effect, hydrocephalus with or without intracranial hypertension, uncontrollable epilepsy and disseminated infiltration of parenchymal cells (functional in a given organ) are among the mechanisms of cognitive deficits in the course of the development of tumours of CNS [11]. The last of the patomechanisms particularly influences cognitive deficits in the course of disseminated neoplasms of CNS. Post mortem examinations of patients with significant cognitive deficits in the course of PCNSL found that the area of parenchymal parts of the brain occupied by the neoplasm was much larger than the one shown in magnetic resonance neuroimaging [12]. The extent of the neoplasm occupation of the brain does not necessarily influence the degree of cognitive deficits in a proportional manner, as some patients with radiologically confirmed localization of neoplastic changes present unchanged functional activity [13].

At first, consulting psychiatry specialists have declared psychomotor disinhibition caused by the neoplastic changes in frontal lobes as a sole cause of violent and risky behaviour presented by the patient. Disinhibition is one of the symptoms included in frontal lobe syndrome, which is typically related to the damage of the frontal lobe area due to injury, ischemic episode, neurodegenerative or neoplastic disease [14]. Frontal lobe syndrome mainly manifests with conduct and psychomotor disorders and its main symptoms include psychomotor agitation, disinhibition, aggression and jocular behaviour – all of them could be observed in the described patient.

At the admission to Department of Psychiatry, the patient was also diagnosed with unspecified delirium. According to ICD-10, delirium is an etiologically nonspecific organic cerebral syndrome characterized by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behaviour, emotion, and the sleep-wake schedule. The duration is variable and the degree of severity ranges from mild to very severe [15]. It is estimated that already at the point of admission, signs of delirium can be found in 11-25% of older (≥ 65 years old) hospitalized patients. Delirium will develop during hospitalization in another 29-31% of these patients [16]. The most significant risk factors of the development of delirium are pre-existing dementia, age above 65 years, coexistence of other diseases and their severity, infections, chronic use of "high-risk" drugs (e.g. benzodiazepines, neuroleptics), as well as immobilization, sensory disorders (especially hearing and vision), catheterization, electrolyte disturbances and malnutrition [17]. Delirium can manifest in hyperactive (agitation, aggression), hypoactive (lowered alertness and motor activity, anhedonia) or mixed form. Hypoactive form is the most common, especially among older patients, while pure hyperactive form is relatively rare. Many authors note the problem of underdiagnosis of hypoactive forms of delirium by hospital staff, which can result in delayed start of adequate treatment [18]. Despite numerous hypotheses being proposed in the literature, the mechanism of delirium formation has not yet been empirically confirmed.

The diagnostic criteria of delirium included in ICD-10 and DSM-5 require clinicians to take into account other, pre-existing or currently developing brain or systemic diseases (other than the influence of psychoactive substances), which may offer a better explanation for attention, consciousness and cognitive deficits [19]. As the described case can present, a disseminated brain tumor with a high proliferation index could have a significant effect on these characteristics. Unfortunately, regardless of the application of modern neuroimaging techniques, it is impos-

sible to assess precisely the influence of the neoplasm on the patient's functioning. Delirium superimposed on dementia is classified in ICD-10 as a separate disorder. Due to the fact that dementia is a strong risk factor for delirium, delirium superimposed on dementia occurs relatively frequently, up to 39% of patients older than 60 years hospitalized in acute mode (in the American population) [20]. In the differential diagnosis of dementia and delirium the time factor is invaluable and should be necessarily considered, both in the analysis of the onset and the further course of the disease. Delirium is characterized by acute onset with fluctuating course ranging from hours to weeks, while dementia typically develops slowly and has chronic, progressive character. Described patient developed dementia symptoms in a relatively short time due to the rapid development of CNS tumor – however, the exact beginning of delirium is not obviously noticeable. The patient may have experienced postoperative delirium, as the criteria allow for the diagnosis up to 5 days after the procedure [18]. According to the patient's wife, the patient behaved differently after the craniotomy, exhibited orientation deficits and lack of contact with the surroundings, which could indicate hypoactive delirium. After some time at home, the patient left the house by himself without sufficient orientation in space, which could indicate the beginning of mixed form of delirium. In like manner, the attempt to jump through the window at Department of Internal Medicine could be considered as an impulsive act of attempting to go out – the patient had resigned from jumping out the window due to the high altitude. In the case of delirium and dementia close in time, the characteristics of symptoms should be useful in differential diagnosis. Attention and orientation impairment and behaviour typical for delirium can be observed only in the late stages of dementia. In contrast to dementia, delirium is characterized by impaired consciousness. In delirium speech is usually incoherent, chaotic, and – depending on the form – slowed down or excessively live, thinking is disorganized with frequent delusions. In dementia, speech impairment can manifest as e.g. difficulties in finding the correct words, while thinking can be seen as sluggish. The perceptual aspect can also differentiate both states – hallucinations and delusions are frequently observed in delirium, while in dementia they occur only in the late stages (in the case of dementia with Lewy bodies, in the early stages) [21].

The multifaceted case of the patient in question may be a demanding diagnostic task for a number of reasons. Due to the rapid growth of primary central nervous system lymphoma, the patient has relatively rapidly developed dementia. Neoplastic changes in frontal lobes were the probable cause of the development of frontal lobe syndrome. The patient also developed delirium without a clearly defined onset. Furthermore, there was a delay in the application of radiotherapy due to retrograde and anterograde amnesia, which resulted in a lack of consent for adequate treatment of cancer and the further disadvantage of the patient. Considering the relatively fast rate of recovery, which could be measured in weeks, the most probable cause of the patient's memory deficits and violent and risky behaviours (such as the attempt to jump out the window) is delirium. However, the patient's other conditions have convoluted the manifestation of delirium and hampered the diagnostic process.

Conflicts of interest: none

REFERENCES

1. Alvarez-Pinzon AM, Wolf AL, Swedberg H, Coy SR, Valerio JE. Primary Central Nervous System Lymphoma (PCNSL): Analysis of Treatment by Gamma Knife Radiosurgery and Chemotherapy in a Prospective, Observational Study. Cureus. 2016; 8(7):e697.
2. Villano JL, Koshy M, Shaikh H, Dolecek TA, McCarthy BJ. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. Br J Cancer. 2011;105(9):1414–1418.
3. Abrey LE. Primary central nervous system lymphoma.Curr Opin Neurol. 2009;22(6):675–680.
4. Schlegel U. Primary CNS lymphoma. Ther Adv Neurol Disord. 2009;2(2):93–104.
5. Schlegel U, Schmidt-Wolf IG, Deckert M. Primary CNS lymphoma: clinical presentation, pathological classification, molecular pathogenesis and treatment. J Neurol Sci. 2000;181(1–2):1–12.
6. Madhusoodanan S, Opler MG, Moise D, Gordon J, Danan D, Sinha A, Babu RP. Brain tumor location and psychiatric symptoms: is there any association? A meta-analysis of published case studies. Expert Rev Neurother. 2010;10(10):1529-36.

7. Madhusoodanan S, Danan D, Moise D. Psychiatric manifestations of brain tumors: diagnostic implications. Expert Rev Neurother. 2007;7(4):343–349.
8. Hollender A, Kvaloy S, Nome O, Skovlund E, Lote K, Holte H. Central nervous system involvement following diagnosis of non-Hodgkin's lymphoma: a risk model. Ann Oncol.. 2002;13(7):1099–1107.
9. Davies E, Clarke C. Early symptoms of brain tumours. J Neurol Neurosurg Psychiatry. 2004;75:1205–1206.
10. Tucha O, Smely C, Lange KW. Effects of surgery on cognitive functioning of elderly patients with intracranial meningioma. Br J Neurosurg. 2001;15:184–188.
11. Omuro AMP, Delattre JY. Brain tumors and dementia. Handb Clin Neurol. 2008;89:877-886. doi:10.1016/S0072-9752(07)01277-8.
12. Lai R, Rosenblum MK, DeAngelis LM. Primary CNS lymphoma: a whole-brain disease? Neurology. 2002;59:1557–1562.
13. Schiffbauer H, Ferrari P, Rowley HA, Berger MS, Roberts TP. Functional activity within brain tumors: a magnetic source imaging study. Neurosurgery. 2001;49:1313–20.
14. Stuss DT, Alexander MP. Executive functions and the frontal lobes: a conceptual view. Psychol Res. 2000;63(3–4),289–298.
15. World Health Organization. (2016). International Statistical Classification of Diseases and Related Health Problems, 10th revision, Fifth Edition.
16. Vasilevskis EE, Han JH, Hughes CG, Ely EW. Epidemiology and risk factors for delirium across hospital settings. Best Pr Res Clin Anaestesiol. 2012;26(3):1-17.
17. Ahmed S, Leurent B, Sampson EL. Risk factors for incident delirium among older people in acute hospital medical units: A systematic review and meta-analysis. Age Ageing. 2014;43(3):326-333.
18. Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. Eur J Anaesthesiol. 2017;34(4):192-214.
19. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC: Author.
20. Brooke J. Differentiation of delirium, dementia and delirium superimposed on dementia in the older person. Br J Nurs. 2018;27(7):363-367.
21. Caplan JP, Rabinowitz T. An Approach to the Patient with Cognitive Impairment: Delirium and Dementia. Med Clin North Am. 2010; 94(6):1103-1116.