CASE REPORT

Hypothalamic relapse of a cardiac large B-cell lymphoma presenting with memory loss, confabulation, alexia–agraphia, apathy, hypsomonia, appetite disturbances and diabetes insipidus

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SUMMARY

A 37-year-old Hispanic man with a right atrial intracardiac mass diagnosed as diffuse large B-cell lymphoma (DLBCL) was successfully treated with surgery and chemotherapy. During 4 years, several total-body positron emission tomography and MRI scans showed no extracardiac lymphoma. On year 5 after the cardiac surgery, patient presented with sleepiness, hyperphagia, memory loss, confabulation, dementia and diabetes insipidus. Brain MRI showed a single hypothalamic recurrence of the original lymphoma that responded to high-dose methotrexate treatment. Correction of diabetes insipidus improved alertness but amnesia and cognitive deficits persisted, including incapacity to read and write. This case illustrates two unusual locations of DLBCL: primary cardiac lymphoma and hypothalamic. We emphasise the importance of third ventricle tumours as causing amnesia, confabulation, behavioural changes, alexia–agraphia, endocrine disorders and alterations of the circadian rhythm of wakefulness–sleep secondary to lesions of specific hypothalamic nuclei and disruption of hypothalamic–thalamic circuits.

BACKGROUND

Primary cardiac lymphoma (PCL) is an extranodal non-Hodgkin’s lymphoma exclusively located in the heart and/or pericardium. According to Maleszewski and Jaffe,1 the term PCL is used when the tumour resides primarily in the heart or presents with predominant cardiac manifestations even when limited extracardiac involvement is present. PCL is a rare cardiac tumour accounting for 1.3% of all primary cardiac tumours.2 In the patient reported here, the primary cardiac diffuse large B-cell lymphoma (DLBCL) was successfully treated with surgery and chemotherapy before itrelapsed in the central nervous system (CNS) 5 years after completion of treatment. The CNS relapse of a PCL is extremely rare and, to our knowledge, of the nine cases previously reported,1-10 none had involvement of deep midline diencephalic structures (table 1).

Third ventricle tumours causing cognitive and behavioural disturbances are rarely described despite having important localising significance. Lesions involving the hypothalamus may manifest clinically with memory deficits and confabulation, endocrine disorders, behavioural changes and alterations of the wakefulness–sleep circadian rhythm. We report a rare case of hypothalamic lymphoma and review the literature to emphasise the importance of amnesia, confabulation, apathy, abulia, alexia, agraphia and sleep disturbances as manifestations of a tumour localised in the medial diencephalon.

CASE PRESENTATION

In 2007, a 37-year-old Hispanic man presented with symptoms of haemodynamic cardiac compromise and was found to have a cardiac mass invading the right atrium and mediastinum. MRI of the chest (figure 1) showed a large right heart mass (8.4×7.4×7.6 cm) centred at the lateral aspect of the right heart near the mitral valve and extending into the pericardial and epicardial fat. The tricuspid valve was deformed by the mass; there was no involvement of the interatrial and interventricular septum. In the resected tissue, the tumour extended up to the base of the tricuspid valve. The mass extended superiorly to the right lateral part of the aortic root and to the lateral aspect of the right ventricular outflow tract.

Initial 2-deoxy-2-(18F)fluoro-D-glucose (FDG-PET) scan showed normal tracer uptake in the brain, nasopharynx, oropharynx, larynx and adjacent structures, including the sternocleidomastoid muscles, without the presence of pathological lymph nodes in the neck. The patient underwent median sternotomy, atrial tumour debulking and tricuspid valve replacement. DLBCL was diagnosed and he completed eight cycles of chemotherapy (R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone)) followed by involved field radiotherapy. About 1 month after completing his radiation therapy, tumour recurrence in the mediastinum was found and he was reinduced with chemotherapy (R-ESHAP (rituximab, etoposide, solumedrol, cytarabine and platinum)) receiving two cycles followed by consolidative high-doses chemotherapy (BEAM (BuCNU Carmustine, Etoposide, Ara-C citarabine, melphalan)) and autologous stem cell support.

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The patient was followed for 4 years with several total-body FDG-PET, CT and MRI scans that showed no extracardiac location of the lymphoma and no evidence of disease recurrence after his bone marrow transplant. In 2012, 5 years after initial presentation of the lymphoma, the patient’s family reported that for the past 3 months, he had exhibited marked memory deficits for recent events, severe daytime sleepiness and behavioural changes such as apathy, loss of interest, lack of energy and hyperphagia.

On examination, the patient was a 42-year-old obese man with normal vital signs. His level of arousal fluctuated with brief periods of alertness followed by intermittent sleep attacks. He knew his name but was disoriented to time and space. He spoke slowly, showed poor recall and confabulated. No focal neurological findings were present and no other neurological abnormalities were found. Lymphoma recurrence in the brain was suspected and CT scan demonstrated a mass in the third ventricle. Brain MRI confirmed a 21×26×25 mm uniform enhancing mass (figure 2) involving the anterior–inferior portion of the third ventricle and adjacent structures, including the hypothalamus, with suprasellar extension. There was no hydrocephalus.

The lymphoma in the heart and mediastinal lymph nodes resected in 2007 was a DLBCL. By flow cytometry, the lymphoma expressed CD10, CD19, CD20 and CD79b. There was kappa light chain restriction and the lymphoma was Epstein-Barr virus (EBV) negative both by in situ hybridisation for EBV-encoded RNA and by immunohistochemistry for EBV latent membrane protein. In 2012, the brain biopsy pathology showed that the tumour was recurrent DLBCL. Flow cytometric immunophenotyping showed a monoclonal B-cell population positive for CD10, CD19 and CD20 with kappa light chain restriction. This immunophenotype is similar to the cardiac tumour and confirmed the cerebral relapse of the PCL.

The patient was successfully reinduced with high-dose methotrexate resulting in disappearance of the brain mass. Afterwards, on several occasions, he was admitted to the emergency room for treatment of electrolyte disturbances with hypernatraemia from diabetes insipidus. Desmopressin treatment optimised sodium levels and hydration, but despite the successful lymphoma treatment, his altered mental status persisted.

Table 1  Reported cases of primary cardiac lymphoma with CNS relapse

| Case no. | Authors | Date   | Age (years)/Sex | Location/Time to CNS relapse |
|---------|---------|--------|-----------------|-----------------------------|
| 1       | Kimura et al | 1997   | 60/F            | Multiple metastases/13 months |
| 2       | Montalbetti et al | 1999   | 51/M            | Meningeal/3 months          |
| 3       | Alzeerah et al | 2003   | 65/M            | Multiple metastases/6 months |
| 4       | Bulum et al  | 2007   | 70/M            | L frontal mass/2 months     |
| 5       | Nishizawa et al | 2010   | 68/F            | Neurolymphomatosis/2 months |
| 6       | Jung et al   | 2014   | 62/M            | R parahippocampal gyrus, thalamus, basal ganglia; ventricular ependyma/1 month |
| 7       | Montoro et al | 2014   | 54/F            | Fourth ventricle/2 months   |
| 8       | Montoro et al | 2014   | 59/F            | L frontal, L parietal/1 month |
| 9       | Soon et al   | 2016   | 75/F            | Neurolymphomatosis/10 months |
| 10      | Ospina-Garcia et al | 2018   | 37/M            | Third ventricle—hypothalamus/5 years |

*This report.

CNS, central nervous system; F, female; L, left; M, male; R, right.

Figure 1  Chest MRI (unenhanced 15 February 2007) showing a large right heart mass extending inside the cardiac lumen and outside into the pericardial and epicardial fat. The tricuspid valve is deformed by the mass.

Figure 2  Brain MRI (gadolinium-enhanced 1 November 2012) showing a 21×26×25 mm enhancing mass involving the anterior inferior third ventricle and adjacent structures including suprasellar extension.
Table 2: Neuropsychological performance at initial treatment of the diencephalic tumour and 15 months later.

| Variable                      | At initial treatment | Fifteen months later |
|-------------------------------|----------------------|----------------------|
| **Dementia screening**        | MMSE                 | MMSE                 |
| **Cognitive domains**         |                      |                      |
| Memory                        | FCSRT                | Logical memory WMS-III |
|                               | Immediate recall     | 0/25                 |
|                               | Delayed recall       | 0/25                 |
|                               | Recognition          | 0/15                 |
| Rey Complex Figure Test—recall| 0/18                 | 1/18                 |
| **Language**                  |                      |                      |
| Boston Naming Test            | 4/50                 | 26/50                |
| Verbal fluency (named in 30 s)| 4/90                 | 5/90                 |
| **Animals**                   |                      |                      |
|                               | 2/12                 | 2/12                 |
| **Word starting with letter 'P'** | 1/12               | 1/12                 |
| **Visual-spatial function**   |                      |                      |
| Rey Complex Figure Test—copy  | 8/18                 | 8/18                 |
| Executive function, attention and speed of processing | | |
| **Trail Making Test**         |                      |                      |
| Part A (sec)                  | 300'                 | 113'                 |
| Mental Control WMS-III        | 8/35                 | 8/35                 |
| Clock Drawing Test            | 3/14                 | 12/14                |
| Cognitive fluctuation         |                      |                      |
| Fluctuation Inventory Scale   | 14/16                | 8/16                 |
| **Other domains**             |                      |                      |
| IADL                          | 0/8                  | 3/8                  |
| Geriatric Depression Scale    | 26/30                | 26/30                |
| Neuropsychiatric Inventory    | 73/144               | 12/144               |

Data are presented as direct scores.
FCSRT, Free and Cued Selective Reminding Test; IADL, Instrumental Activities of Daily Living Scale; MMSE, Mini-Mental State Examination; WMS-III, Wechsler Memory Scale, Third Edition.

INVESTIGATIONS, TREATMENT AND OUTCOME

In 2013, we evaluated the patient at the Memory & Dementia Clinic of the Houston Methodist Neurological Institute due to persistent memory loss, confabulation, sleepiness, abulia, apathy and crying spells. Continuous electroencephalographic (EEG) recordings during the neuropsychological evaluation showed sleep attacks with fluctuating attention. Patient was disoriented to time, space and person. Spanish language evaluation revealed semantic paraphasias and word-finding difficulties. His main problem was the severe abnormality of verbal and visual memory, poor recall of recent events, episodic memory deficits and confabulations during the assessment (table 2). The neuropsychological performance indicated global cognitive loss and executive dysfunction consistent with moderate to severe dementia.

Neurological examination confirmed the changes in alertness, cognition and mental status. Visual fields and extraocular movements were normal, and there were no alterations of motor or sensory functions. Deep tendinous reflexes and coordination were normal. MRI showed no evidence of the hypothalamic mass (figure 3). The patient presented apathy, depression and pseudobulbar crying spells; he received treatment with dextromethorphan–quinidine (Nuedexta) and sertraline with improvement of these symptoms. Obstructive sleep apnoea was demonstrated and treated with nasal continuous positive airway pressure resulting in control of the excessive daytime sleepiness.

He returned 1 year later and his cognitive functions had improved; memory and learning difficulties persisted but confabulation was no longer evident. He was last seen in the clinic in 2017 (ie, 10 years after onset of cardiac symptoms and 5 years after the CNS relapse); at that time, there was no evidence of tumour recurrence. He had returned to gainful manual work despite the persistence of the amnesia and the fact that he had forgotten how to read and to write, notwithstanding speech and cognitive therapy.

DISCUSSION

According to the WHO, DLBCL represents 25%–30% of adult non-Hodgkin lymphomas. PCL is a rare extranodal localisation and CNS dissemination is exceptional. The 2015 AFIP (Armed Forces Institute of Pathology) criteria include cases of lymphoma presenting with cardiac manifestations, particularly if the bulk of disease is found in the heart or the pericardium. Thus, despite the mediastinal lymph node involvement in our case, the tumour was diagnosed as PCL. CNS relapses of primary cardiac DLBCL are rare and probably due to genetic factors, including dual translocations of MYC and BCL2 (so-called ‘double-hit DLBCL’). In the case reported here, we present an in-depth analysis of the complex cognitive and behavioural symptoms manifested by this patient, providing clinicopathological correlations with relevant anatomic structures of thalamus and hypothalamus.

Memory loss

In 1937, James W. Papez, described the basic memory circuit comprising the hippocampus and structures in the neighbourhood of the third ventricle including fornix, mammillary bodies, the mamillothalamic tract of Vicq-d’Azyr, as well as the anterior and medial thalamic nuclei. The subiculum and presubiculum in the hippocampal formation project to the anteromedial, anterodorsal and anteroventral thalamic nuclei as well as to the mammillary bodies via the fornix. From the mammillary bodies, the mamillothalamic tract provides input to the anterior thalamic complex which then projects to cingulate, orbitofrontal, retrosplenial and subicular areas. Injury to any of these structures can result in severe anterograde memory loss, affecting especially episodic and recognition memory. Left medial thalamic lesions cause verbal
memory deficits, while right-sided lesions result in loss of visuospatial memory.\textsuperscript{18}

In the patient reported here, the tumour lesion in the walls of the third ventricle caused alterations primarily in episodic memory, severe learning impairment and difficulties with recall of both verbal and visual information, probably explaining the loss of the capacity to read and write without evidence of language disruption.\textsuperscript{19} These deficits correlate with the midline localisation of the lesion affecting bilaterally the fornix, without involvement of the mammillary bodies but perhaps with involvement of the anterior thalamic complex and dorsomedial nucleus.

In 1967, Georges de Morsier,\textsuperscript{20} reported a similar case of amnestic syndrome in a patient with a hypothalamic glioma; the lesion was bilateral, involved the mammillary bodies and the fornix and had mesencephalic extension confirmed by neuropathology.\textsuperscript{20} He reviewed the cognitive and clinical presentation in 38 cases of hypothalamic tumours from the literature including his case. Men predominated (58%) and the median age was 45.1 years (range, 19–62); 37% were older than 41 years. The tumours included craniopharyngiomas (58.2%), gliomas (13.9%), chromophobe adenomas (11.1%), ependymal cysts (5.6%), metastases (5.6%), eosinophilic adenomas (2.8%) and teratomas (2.8%). Duration of the symptom ranged from 2 to 8 years for teratomas, adenomas and ependymal cysts, and from weeks to months in the remaining lesions. According to de Morsier,\textsuperscript{21} the amnestic syndrome was present in 100% of the cases followed by: (1) behavioural problems, including manic changes and euphoria, lack of social inhibition, depression, anxiety, apathy and irritability (84.2%); (2) confabulation and false recognitions (53%); (3) excessive daytime somnolence (47.4%); (4) motor symptoms such as facial spasms, dysarthria, hypotonia, catalepsy and parkinsonism (36.8%); (5) hypersexuality or loss of libido (31.6%); (6) hyperphagia, obesity, polydipsia and polyuria (31.6%); and (7) visual hallucinations (18.4%) consistent with vivid dreams. With the exception of motor symptoms and hallucinations, all the other manifestations were present in our case.

Confabulation

In addition to amnesia, this patient had confabulation whereby he provided obviously false information in response to simple questions. Confabulation is a common symptom in acute Wernicke-Korsakoff syndrome and in patients with ruptured aneurysms of the anterior communicating artery implicating well-defined brain structures in the pathogenesis of this symptom. The neuropathology of acute alcoholic Wernicke’s encephalopathy from thiamine (vitamin B\textsubscript{1}) deficiency most frequently involves the mammillary bodies with presence of microhaemorrhages.\textsuperscript{21} In patients with Korsakoff amnestic syndrome—considered a chronic residual manifestation of Wernicke’s encephalopathy—the neuroanatomical lesion that appears to account for the amnesia is damage to the anterior nucleus of the thalamus secondary to involvement of the mammillary bodies.\textsuperscript{22}

In this patient, there was no apparent damage to the mammillary bodies and both hippocampi were intact suggesting that the bilateral injuries of the fornix and minor involvement of the anterior thalamic nuclei were probably responsible for the amnesia and the transient confabulation. It has been postulated that confabulations occur when the preserved hippocampus receives distorted information from other areas of the brain, especially prefrontal medial and orbitofrontal areas or their projections.\textsuperscript{23} The latter structures are important for strategic retrieval that involves search processes and monitoring of the memories. It has been hypothesised that confabulations are produced by failures in retrieval process and selection of memories within a specific time and context.\textsuperscript{24}

**Apathy, abulia, irritability**

Apathy can be observed mainly with anterior cingulate damage although it may also occur with lesions in nucleus accumbens, ventral pallidum, ventral segmental area and medial dorsal nucleus of the thalamus.\textsuperscript{3} Disruption along the cortico-striatal-pallidal-thalamic-cingulum circuits produces akinetic mutism, abulia or apathy depending on the grade of severity of the dysfunction.\textsuperscript{26} In our patient, the apathy, lack of self-initiated action, decreased responsiveness to stimuli and irritability could have resulted from disruption of thalamic projections to the cingulate cortex and to the orbitofrontal medial cortex. Nishio \textit{et al},\textsuperscript{27} studied patients with left anterior thalamic infarcts using combined FDG-PET and MRI stereotactic localisation; apathy was found in all cases, along with verbal memory impairment and language disturbances, in particular anoma and word-finding difficulties. FDG-PET showed decreased regional cerebral blood flow perfusion of the left anterior cingulate gyrus.\textsuperscript{28} In contrast, right thalamic lesions leading to disruption of the right orbitofrontal circuit presented with irritability and socially unacceptable behaviours,\textsuperscript{29} similar to those of frontal lobe syndrome.\textsuperscript{30}

**Pseudobulbar affect**

Our patient presented with crying spells and faulty control of emotional impulses; this syndrome is currently classified as pseudobulbar affect (PBA) and is thought to arise from disruption of corticobulbar and cerebellopontine pathways controlling emotional expression.\textsuperscript{31} In our case, disruption of projections from the anteromedial thalamus to orbitofrontal cortex could be responsible for the PBA.\textsuperscript{32} In general, lesions in subcortical segments of these anatomical systems by a tumour mass in the third ventricle often cause mixed syndromes because of the proximity of multiple subcortical structures involved in the different circuits.\textsuperscript{32} Dextromethorphan plus ultra-low-dose quinidine\textsuperscript{33} reduced PBA and had a positive effect in our patient. Dextromethorphan\textsuperscript{34} is an uncompetitive N-methyl-D-aspartate receptor antagonist, a sigma-1 receptor agonist and a serotonin reuptake inhibitor.

**Loss of reading and writing ability: alexia–agraphia**

Our patient lost the previously learnt capacity to read and write, and despite intense cognitive therapy, he has been unable to read; he cannot go beyond the letter B when trying to repeat the alphabet. In 2013, Barker \textit{et al},\textsuperscript{18} reported here a similar case in an 18-year-old man with a third ventricle colloid cyst who became symptomatic after a minor traumatic brain injury. The authors demonstrated that the cyst had splayed the fornix interfering with memory recall. As in our patient, in their case, there was no involvement of visual pathways nor of cortical areas usually implicated in alexia and agraphia such as lesions of the lingual gyrus or fusiform gyrus (respectively, medial and lateral occipitotemporal gyri) thought to mediate letter and word recognition. Given our patient’s profound memory loss, this case would support the pathogenesis of some forms of alexia–agraphia from bilateral injury of fornix tracts in the third ventricle.
Sleep disturbances

Besides the cognitive and behavioural symptoms, our patient had important alterations in wakefulness with excessive daytime sleepiness resulting from diurnal sleep attacks demonstrated by prolonged EEG recording. Specific neuronal populations located in the basal forebrain and the hypothalamus control the regulatory mechanisms for the initiation and control of sleep–wake cycles, as well as for alternation between the different sleep stages.35 36 As mentioned earlier, almost half (47.4%) of the patients with third ventricle tumours and paramedian thalamic lesions have daytime hypersomnia.20 In these cases, rapid-eye movement (REM) sleep is usually normal, but wakefulness, sleep spindling and delta waves are all reduced, suggesting that the medial thalamus mediates wakefulness and promotion of non-REM sleep.37 The anterior hypothalamic neurons (orexin, melanin-concentrating hormone) that are activated during REM sleep are located in the posterior hypothalamus and anterior hypothalamic areas such as the supraoptic and paraventricular nuclei, mediobasal hypothalamus.43 Currently, although we failed to quantify cerebrospinal fluid (CSF) levels of the wake-promoting neuropeptide orexin, the residual diabetes insipidus was controlled with desmopressin.43–46 Diabetes insipidus results in excretion of large volumes of diluted urine leading to hypernatraemia. In addition to polyuria, our patient also had abnormal blood glucose levels. These symptoms are the consequences of involvement of specific hypothalamic areas such as the supraoptic and paraventricular nuclei, and the mediobasal hypothalamus.43 Currently, the patient requires desmopressin to maintain homeostasis of the electrolytic balance and needs strict glucose control.

In conclusion, we present the results of the complete evaluation and treatment of a patient with a primary cardiac lymphoma (DLBCL) that responded to surgical treatment and aggressive medical oncology therapy of the primary lesions in the heart and mediastinum but had a brain relapse 5 years later involving selectively the walls of the third ventricle.

**Table 3**

| Anatomical structure* | Symptoms |
|-----------------------|----------|
| Fornix (bilateral tracts) and projections to anterior thalamic nuclear complex and dorsomedial thalamic nucleus | Amnesia: episodic memory loss for verbal and visual information; learning impairment |
| Fornix and anterior thalamic complex | Confabulation |
| Thalamic projections to cingulate cortex and orbitofrontal medial cortex | Apathy, lack of self-initiated action |
| Thalamic projections to orbitofrontal cortex | Pseudobulbar affect, crying spells |
| Fornix tracts | Alexia–agraphia |
| Medial thalamus, anterior hypothalamic cholinergic and GABAergic neurons | Sleep attacks, alteration of circadian rhythm of wakefulness–sleep |
| Lateral hypothalamic neurons (orexin, melanin-concentrating) | Hyperphagia, alteration of appetite |
| Ventromedial hypothalamic nucleus, arcuate nucleus | Diabetes insipidus responsive to desmopressin |
| Supraoptic and paraventricular nuclei, mediobasal hypothalamus (arginine vasopressin) | |

* Nomenclature according to: Swaab DF. The Human Hypothalamus: Basic and Clinical Aspects. Part I: Nuclei of the Human Hypothalamus. Handb Clin Neurol 2003;79:1–597.

Endocrine disturbances

The most common hypothalamic endocrine disturbance is diabetes insipidus due to inadequate production and release of the antidiuretic hormone arginine vasopressin.43 Diabetes insipidus results in excretion of large volumes of diluted urine leading to hypernatraemia. In addition to polyuria, our patient also had abnormal blood glucose levels. These symptoms are the consequences of involvement of specific hypothalamic areas such as the supraoptic and paraventricular nuclei, and the mediobasal hypothalamus.43 Currently, the patient requires desmopressin to maintain homeostasis of the electrolytic balance and needs strict glucose control.

Control of appetite

Apart from the disturbances mentioned above, our patient had alterations in feeding behaviour, especially hyperphagia and weight gain. Localised hypothalamic lesions involving ventromedial hypothalamus (VMH) and arcuate nucleus have been associated with hyperphagia and obesity in humans. A neoplastic lesion involving the midline hypothalamus resulting in bilateral destruction of the VMH area was reported as a cause of hyperphagia.39 About 25%–45% of VMH neurons have glucoreceptors that are activated during feeding to initiate satiety and to decrease food intake. Additionally, arcuate nucleus pro-opiomelanocortin neurons activate VMH neurons.40 Neuronal damage to either arcuate nucleus or VMH neurons may result in hypothalamic obesity.41 42
Contributors HAP designed the initial oncological treatment of the patient and successfully managed the relapses and the internal medicine complications. MRS performed the pathology studies of the cardiac and hypothalamic lesions. GCR evaluated the neurological complications, imaging results and sleep data, and directed the neuropsychiatric treatment. BP performed the neuropsychological evaluations. NO-G summarised the medical records, reviewed the literature and wrote the initial version of the paper in conjunction with GCR. All the authors approved the final manuscript.

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