AKDENİZ SAĞLIK BİLİMLERİ
GÜNCEL ARAŞTIRMALAR DERGİSİ
MEDITERRANEAN JOURNAL OF
HEALTH SCIENCES AND CURRENT RESEARCH
OPEN ACCESS

CASE REPORT

Examination of Neurological Deficits Due to Chemotherapy in a Patient with Nasopharyngeal Tumor

Gökhan Doğukan AKARSU[1], Onur BULUT[2]

DOI: https://doi.org/10.5281/zenodo.13354456

[1]Yozgat Bozok University, School of Health Services,Department of Pharmacy Services, Yozgat/Turkey,

[2]Gazi University Faculty of Medicine, Algologia Department, Ankara,Turkey,

Corresponding Author;
Gökhan Doğukan Akarsu
gokhan_dogukan_akarsu@hotmail.com

Abstract

Nasopharyngeal carcinoma is a complex type of cancer, particularly associated with Epstein-Barr virus infection. In studies conducted in Turkey, this rare cancer typically involves a complex and challenging treatment process. However, this treatment process can sometimes encounter unexpected difficulties. In this article, the neurological conditions experienced by a 62-year-old female patient during the treatment of nasopharyngeal cancer are examined. The patient's restricted iris movement during treatment and subsequent weakness in the right arm and leg illustrate the complexity of the treatment's side effects. Imaging studies revealed serious issues such as brain edema and myelin damage. Additionally, changes in blood clotting ability due to chemotherapy were found to worsen the patient's condition. In conclusion, this article provides an important perspective on the unexpected challenges patients may face during cancer treatment and the impact of these challenges on the treatment process. It emphasizes the necessity of a multidisciplinary approach to better understand and manage patients' treatment processes.

Keywords: Nasopharyngeal Carcinoma, Cancer, Side Effect, Disability.

Received Date:
13.04.2024

Accepted Date:
16.05.2024

Publishing Date:
30.06.2024

Introduction

Nasopharyngeal carcinoma (NPC) is a type of cancer originating from the tissues of the nasopharynx. The tumor usually begins near the Rosenmüller fossa and from this point can affect surrounding anatomical spaces or organs. Despite having similar cells or tissues, there are significant differences between nasopharyngeal carcinoma and other epithelial tumors in the head and neck region (Chua et al., 2016). Morphologically, nasopharyngeal carcinoma is considered to be of squamous origin. There is a strong association between Epstein-Barr virus (EBV) infection and nasopharyngeal carcinoma (Chua et al., 2016). Recent research suggests that the disruption of p16 activity and overproduction of cyclin D1, along with the preservation of the viral genome, promote the progression from low-grade dysplasia to high-grade lesions by diminishing the efficacy of cell cycle checkpoints (Loet al., 2012; Tsang et al., 2012).

In a study conducted in Turkey, the incidence of nasopharyngeal carcinoma was reported to be 0.7% of all cancer cases (Aksoy, 2018). The treatment processes for nasopharyngeal carcinoma are carried out according to protocols prepared by oncology units. These protocols involve various methods such as radiotherapy, chemotherapy, and other treatments, depending on the individual patient.

Case Report

Our patient is a 62-year-old woman. We have been following our patient since 18/03/2024. However, since there is no oncology unit in the hospital we are in, oncology treatments are followed by a tertiary healthcare institution in another province. The data of our patient's medical history and all health procedures performed have been obtained from the e-Nabız application with the patient's consent. In May 2021, she presented to primary and secondary healthcare providers due to swelling in her neck and was diagnosed with nasopharyngeal carcinoma in August of the same year. At the time of diagnosis, the cancer was at stage 4 with metastases to the right humeral head, sternum, and sacral region. The patient underwent chemotherapy with Cisplatin at a dose of 100 mg/dl. Concurrently, radiotherapy was administered. PET-CT scans showed that the chemotherapy agents were effective, but the cancerous tissues remained active, leading to the continuation of chemotherapy with Cisplatin. During this phase, the patient developed middle ear otitis, resulting in hearing issues.

After the chemotherapy ended, the patient awaited PET-CT scans but lost her residence during the earthquake on February 6, 2023, rendering her unable to access healthcare services for a period. On the day of the earthquake, she noticed that she could not move her right iris outward, potentially due to trauma or another cause. Subsequent examinations revealed nerve damage in the

extraocular muscles. Despite regular check-ups, the movement restriction in her eye persisted for 15 months. In the new city where she relocated, the oncology unit initiated oral chemotherapy (2300 mg/day), and no surgical operation was performed for the eye during the treatment. Additionally, in September 2023, the patient underwent surgery to remove a malignant lymph node located behind the manubrium sterni and in front of the ascending aorta. Following this, a PET-CT scan detected malignant lymph nodes in the posterior mediastinum, inferior to this lymph node, and in the right bronchial hilum. The patient resumed chemotherapy with the same oral agent, administered in a cycle of 14 days on and 7 days off, continuing for 6 cycles.

From the fourth cycle chemotherapy treatment, the patient began experiencing weakness in her right arm and leg. Despite evaluations from various departments, the cause of the weakness remained undetermined. The oncology unit emphasized the importance of continuing chemotherapy without interruption. Neurological and neurosurgical examinations were conducted, and both contrast and non-contrast MRI, as well as MRI spectroscopy, were performed.

Radiological Examinations:

Radiological imaging revealed that bilateral optic nerves had normal thickness and signal properties, the optic chiasm had normal shape and signal properties, and no lesions were found. There was widespread swelling at the C3-4, C4-5, C5-6, and C6-7 levels and increased cervical lordosis with narrowing of the anterior cerebrospinal fluid (CSF) space. There was marked edema, enlargement, and enhancement in the central and dorsal pons extending from the left cerebral crus of the midbrain to the central medulla oblongata. Lesions characterized by weak hypointense signals on T1 sequences and weak hyperintense signals on T2 FLAIR sequences were observed in the lower part of the pons, adjacent to the medulla oblongata and below the left basal ganglia, connected via the brainstem. MR spectroscopy showed moderate increases in choline and NAA activity without changes in creatine activity; This has been reported to be suggestive of Wallerian degeneration. No diffusion restriction area was found in diffusion MRI, but ischemic gliotic lesions were shown to be observed in the white matter.

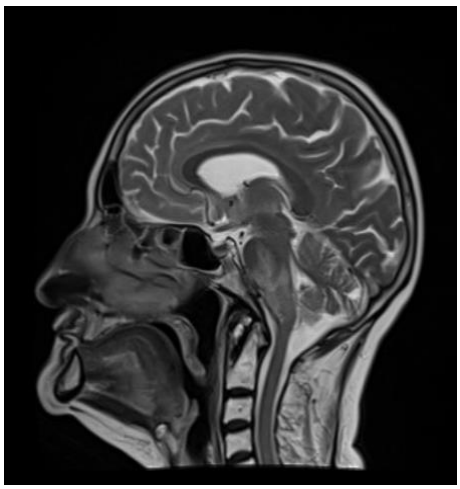

Figure 1. Left side of brain

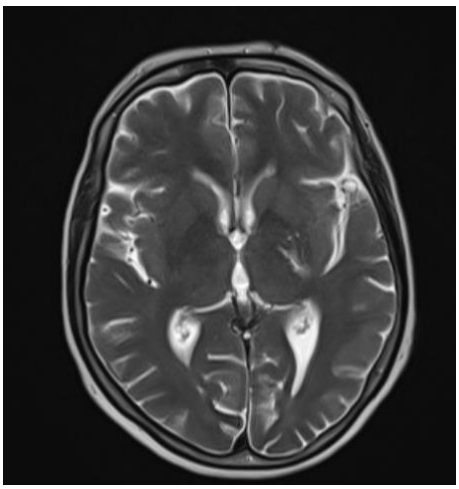

Figure 2. Top view of the brain 1

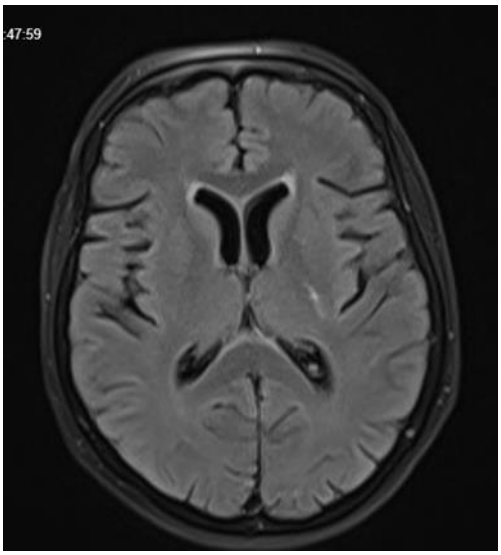

Figure 3. Top view of the brain 2

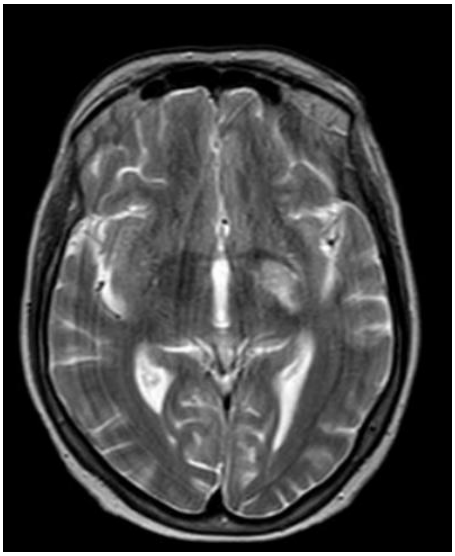

Figure 4. Top view of the brain 3

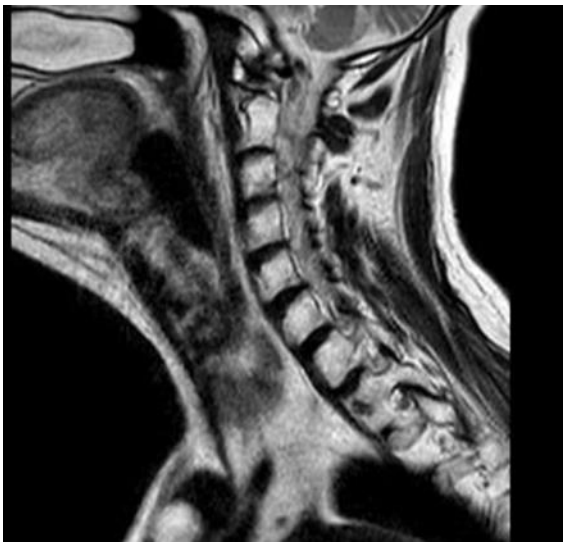

Figure 5. Left side of neck

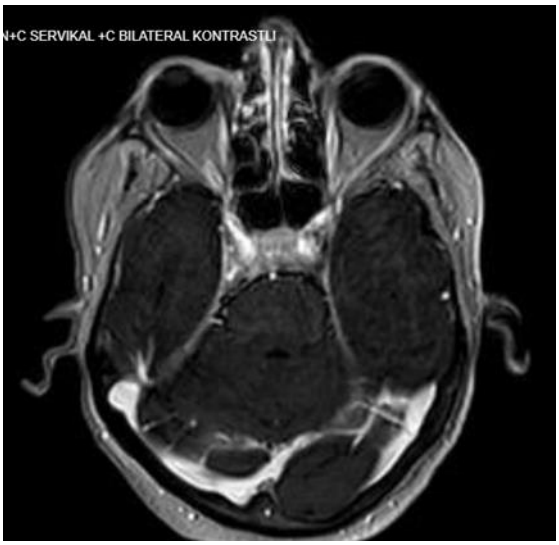

Figure 6. Brain MRI image

Biochemical Examination:

Biochemical analysis results from before the nasopharyngeal carcinoma diagnosis, at the onset of symptoms, and during the use of 2 cycles of Cisplatin and 2 cycles of the oral chemotherapeutic agent are presented in Table 1.

Table 1. Biochemical Analysis Data Tracked Throughout the Patient's Treatment Process

	2.11.2020	**23.06.2021**	**6.09.2021**	**3.01.2022**	**22.06.2022**	**15.02.2023**	**13.07.2023**	**18.03.2024**	**15.04.2024**
Calcium (Ca) mg/dL N(8.5 - 10.6)	9.70	9.30	9.60	9.80	9.80	9.72	9.30	11.08	9.98
Potassium (K) mmol/L N(3.5 - 5.2)	4.40	4.17	4.20	4.48	3.80	4.00	3.90	4.26	4.27
Sodium (Na) (serum) mmol/L N (136 - 148)	138.00	142.00	141.00	142.00	140.00	139.88	142.00	140.00	137.00
Magnesium (Mg) mg/dL N (1.6 - 2.6)	null	2.10	null	2.00	null	1.75	null	1.90	1.68
Phosphorus (P) mg/dL N (2.7 - 4.3)	null	2.90	null	3.40	null	3.00	2.70	3.56	2.87
Chloride (Cl) mmol/L N (98 - 107)	null	106.00	104.00	103.00	null	null	109.00	null	99.50
Iron binding capacity µg/dL N (120 - 370)	null	334.00	320.00	null	225.00	null	null	null	null
Ferritin ng/mL N (15 - 400)	null	34.00	56.80	null	41.50	null	null	null	null
Glucose mg/dL N (70 - 105)	95.00	117.00	75.00	137.00	122.00	99.90	79.00	83.00	153.70

Glycated Hemoglobin (HbA1C) % N (4.8 - 5.9)	null	null	null	null	null	null	null	null	5.02
Creatinine mg/dL N (0.5 - 1.1)	0.71	64.00	0.70	0.80	1.43	0.92	0.88	0.92	1.01
Albumin g/dL N (3.5 - 5.5)	4.20	4.00	4.20	4.50	null	4.19	3.80	4.00	4.46
Blood Urea Nitrogen (BUN) mg/dL N (15 - 45)	30.00	14.49	11.68	12.15	47.70	17.59	32.50	15.68	null
Total Bilirubin mg/dL N (0.2 - 1.2)	0.90	0.70	null	0.60	null	0.65	0.36	0.96	null
Alkaline Phosphatase U/L N (40 - 150)	156.00	146.00	131.00	128.00	null	127.60	92.00	106.00	null
Aspartate Transaminase (AST) U/L N (0 - 35)	22.00	15.00	17.00	12.00	13.00	12.60	12.00	16.00	null
Gamma-Glutamyl Transferase (GGT) U/L N (9 - 36)	18.00	17.00	20.00	18.00	null	13.90	12.00	13.00	null
Alanine Aminotransferase (ALT) U/L N (0 - 35)	20.00	12.00	13.00	11.00	6.00	4.20	5.00	4.00	null
Amylase U/L N (20 - 120)	124.00	null	null	113.00	null	64.80	72.00	88.00	null

Creatine Kinase (CK) U/L N (29 - 168)	110.06	0.80	null	null	null	null	43.25	null	null
CK-MB U/L N (0 - 25)	12.00	null	null	null	null	null	9.70	null	null
Lactate Dehydrogenase (LDH) IU/L N (90 - 250)	309.00	224.00	208.00	189.00	155.00	194.40	147.00	227.00	null
CRP (Turbidimetric) mg/dL N (0 - 0.5)	0.89	0.73	0.95	null	< 0.2	null	< 2.0	null	null
Protein (serum) g/dL N (6.4 - 8.3)	7.80	7.60	8.00	7.70	null	7.82	null	7.50	7.14
Uric Acid mg/dL N (2.6 - 6)	null	4.90	5.10	3.90	6.50	4.27	5.30	4.62	null
TSH mIU/mL N (0.38 - 5.33)	null	null	1.16	null	1.52	null	null	null	1.67
Free T4 ng/dL N (0.61 - 1.12)	null	null	0.82	null	1.14	null	null	null	null
Free T3 pg/mL N (0.86 - 2.49)	null	null	null	null	2.69	null	null	null	null
APTT seconds N (27 - 45)	24.30	null	25.20	null	null	null	21.80	null	20.20
Vitamin B12 pg/mL N (105 - 605)	null	207.00	90.00	null	496.00	null	null	null	494.10
Folate ng/mL	null	13.36	12.07	null	5.98	null	null	null	8.11

N (5.9 - 24.8)									
25-Hydroxy Vitamin D ng/mL N (0 - null)	null	null	null	null	null	null	null	null	13.86
Fibrinogen mg/dL N (150 - 350)	null	347.34	319.99	null	null	null	null	null	null
IgM (Nephelometric) mg/dL N (33 - 293)	null	115.80	null	null	null	null	null	null	null
IgA (Nephelometric) mg/dL N (33 - 293)	null	404.40	null	null	null	null	null	null	null
IgG (Nephelometric) mg/dL N (552 - 1631)	null	1273.90	null	null	null	null	null	null	null
Carcinoembryonic Antigen (CEA) ng/mL N (0 - 3)	null	1.33	1.25	1.32	2.34	2.19	2.88	null	null
Triglycerides (Serum/Plasma) mg/dL N (0 - 200)	null	null	null	null	null	null	null	null	126.40
HDL Cholesterol mg/dL N (45 - 65)	null	null	null	null	null	null	null	null	71.2
Cholesterol (Serum/Plasma) mg/dL N (3 - 200	null	null	null	null	null	null	null	null	209.90

In the biochemical data of our patient, no significant changes were observed due to close monitoring during chemotherapy. However, when examining the biochemical data during the period of muscle weakness in the right arm and leg, a notable decrease in the activated partial

thromboplastin time (APTT) test was observed. Initially, at the onset of the illness, the clotting time was 24.3 seconds and remained unchanged during the first and second chemotherapy sessions. However, during the administration of the third and fourth chemotherapy cycle agents, a significant decrease to 20.2 seconds was noted in APTT. No significant changes were observed in the other biochemical parameters

Discussion

Nasopharyngeal carcinoma (NPC) continues to be prevalent worldwide, representing 0.6% of all cancer cases (Lo et al., 2012). The incidence rate in Turkey is 0.7%, slightly above the world average (0.6%) (Aksoy 2018).Chemotherapy and radiotherapy are effective against NPC and often elicit significant responses. However, treatment can sometimes be less effective than anticipated due to drug dosage, method of administration, malignant cell resistance, or patient-related factors. In this case, we explore the causes behind the patient's neurological deficits, including restricted eye muscle and nerve movement and progressive weakness in the right arm and leg, potentially influenced by both drug effects and the major disruption caused by an earthquake (Pearce et al., 2017; Martino et al., 2014 Brzeziński 2014.

Globally, earthquakes, especially those with magnitudes above 7, have profound psychological and physiological impacts on individuals. The recovery from post-traumatic stress, emotional normalization after loss, and the return to daily life can take a considerable amount of time. Our patient lost her residence in the earthquake, and the oncology services she relied on were disrupted. During the immediate aftermath, access to medications and medical supplies was severely limited, exacerbating the interruption in her treatment. Before the earthquake, the patient had no complaints regarding her eye. Following the earthquake, she reported an inability to move her right eye outward, likely due to trauma. Post-traumatic stress disorder (PTSD) is common after life-threatening events such as cancer, acute coronary syndromes, and natural disasters like earthquakes, varying across different populations (Donkor, 2018; Dückers, Alisic, & Brewin, 2016; Edmondson, 2014).

Stroke is the second most common cause of death globally, with 50% of survivors experiencing permanent disability (Donkor, 2018). Due to the chaos after the earthquake, no imaging or diagnosis could confirm whether the patient's eye movement loss was related to a stroke. Later examinations found no nerve damage.

Approximately a year after the eye movement issue, the patient reported weakness in her right arm and leg. MRI revealed significant edema in the central and dorsal pons. There were no signs of cancer metastasis or a new tumor, but radiology indicated Wallerian degeneration, a

process where distal axons degenerate following trauma (Waller, 1850). This edema might have caused myelin damage, leading to the patient's weakness. The patient had no history of diabetes or hypertension (Barz, Schreiber, & Barz, 2017).

Tissue pressure increases in swollen organs because of the elastic properties of cell membranes and fibrous tissues, which include elastic and collagen fibers and neuronal and glial fibers in the brain. The myelin sheaths of axons, the vascular network, and the meninges exhibit specific elastic characteristics vessels (Barz, Schreiber, & Barz, 2017; Christ et al., 2010; Kaster, Sack, & Samani, 2011).

The central areas of the pons are neuron-rich and swell significantly under cytotoxic edema, impacting the surrounding myelinated fibers, causing severe ischemia (Barz, Schreiber, & Barz, 2017). It has been stated that the cause of myelinolysis may be due to edema and ischemia. (Martin, 2004) Edema is said to choke the myelin sheaths and small blood vessels (Messert et al., 1979). Edema and tissue pressure are two conditions that support each other. Metastatic tumors or major hemorrhages often cause widespread edema in the adjacent brain tissue (Zheng et al., 2016).

Our patient also exhibited a progressive decrease in APTT levels, suggesting increased coagulation tendency, potentially causing hypoxic conditions in the pons, leading to tissue damage and increased edema (Lippi et al., 2010; Sørensen & Ingerslev, 2012). This, in turn, could explain the weakness in the right arm and leg due to myelin sheath damage. Research indicates that shortened APTT times are linked to increased clotting tendency, potentially elevating the risk of thromboembolic events by at least tenfold (Korte et al., 2000; McKenna et al., 1977).

Therefore, we hypothesize that the patient experienced thromboembolic events due to shortened APTT levels from chemotherapy agents, leading to tissue damage and edema in the pons, resulting in myelin sheath damage and subsequent weakness in the right arm and leg. However, as the patient continues chemotherapy, we cannot undertake any invasive or non-invasive interventions.

Conclusion

Chemotherapy is a commonly used treatment for cancer, with varying effects on different patients. Major traumas like earthquakes and treatment interruptions can lead to undesirable outcomes in cancer patients. While the increased coagulation tendency from chemotherapy agents alone might not explain all the effects observed in our patient, we suggest incorporating routine APTT and brain MRI imaging into treatment protocols for chemotherapy patients to better monitor and manage potential complications.

Ethical aspect of research

During the current research, we acted within the framework of the "Higher Education Institutions Scientific Research and Publication Ethics Directive".

Author Contributions

The authors contributed equally to the preparation of the article.

Declaration of competing interests

The authors declare that they have no conflict of interest and that the content has not been published or submitted for publication elsewhere.

Acknowledgments

We express our deepest gratitude to our patient who participated in our study and shared all her data with us.

References

Aksoy S. Nazofarinks Kanserlerinde Sistemik Tedaviler. Turkiye Klinikleri Medical Oncology-Special Topics. 2018;11(2):181-4.

Barz, H., Schreiber, A., & Barz, U. (2017). Demyelinating diseases as a result of cerebral edema? Medical hypotheses, 104, 10-14.

Brzeziński, K. (2012). Chemotherapy-induced polyneuropathy. Part I. Pathophysiology [Polish version: Polineuropatia wywołana chemioterapią. Część I. Patofizjologia p. 79]. Contemporary Oncology/Współczesna Onkologia, 16(1), 72-85.

Christ, A. F., Franze, K., Gautier, H., Moshayedi, P., Fawcett, J., Franklin, R. J., . . . Guck, J. (2010). Mechanical difference between white and gray matter in the rat cerebellum measured by scanning force microscopy. Journal of biomechanics, 43(15), 2986-2992.

Chua, M. L., Wee, J. T., Hui, E. P., & Chan, A. T. (2016). Nasopharyngeal carcinoma. The Lancet, 387(10022), 1012-1024.

Donkor, E. S. (2018). Stroke in the century: a snapshot of the burden, epidemiology, and quality of life. Stroke research and treatment, 2018.

Dückers, M. L., Alisic, E., & Brewin, C. R. (2016). A vulnerability paradox in the cross-national prevalence of post-traumatic stress disorder. The British Journal of Psychiatry, 209(4), 300-305.

Edmondson, D. (2014). An enduring somatic threat model of posttraumatic stress disorder due to acute life-threatening medical events. Social and personality psychology compass, 8(3), 118-134.

Kaster, T., Sack, I., & Samani, A. (2011). Measurement of the hyperelastic properties of ex vivo brain tissue slices. Journal of biomechanics, 44(6), 1158-1163.

Korte, W., Clarke, S., & Lefkowitz, J. B. (2000). Short activated partial thromboplastin times are related to increased thrombin generation and an increased risk for thromboembolism. American journal of clinical pathology, 113(1), 123-127.

Lippi, G., Salvagno, G. L., Ippolito, L., Franchini, M., & Favaloro, E. J. (2010). Shortened activated partial thromboplastin time: causes and management. Blood coagulation & fibrinolysis, 21(5), 459-463.

Lo, K.-W., Chung, G. T.-Y., & To, K.-F. (2012). Deciphering the molecular genetic basis of NPC through molecular, cytogenetic, and epigenetik approaches. Paper presented at the Seminars in cancer biology.

Martino, A., Krainik, A., Pasteris, C., Hoffmann, D., Chabardes, S., Berger, F., ... & Grand, S. (2014). Neurological imaging of brain damages after radiotherapy and/or chimiotherapy. Journal of Neuroradiology, 41(1), 52-70.

Martin, R. (2004). Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes. Journal of Neurology, Neurosurgery & Psychiatry, 75(suppl 3), iii22-iii28.

McKenna, R., Bachmann, F., & Miro-Quesada, M. (1977). Thrombo-embolism in patients with abnormally short activated partial thromboplastin time. Thrombosis and haemostasis, 38(08), 0893-0899.

Messert, B., Orrison, W. W., Hawkins, M. J., & Quaglieri, C. E. (1979). Central pontine myelinolysis Considerations on etiology, diagnosis, and treatment. Neurology, 29(2), 147-147.

Pearce, A., Haas, M., Viney, R., Pearson, S. A., Haywood, P., Brown, C., & Ward, R. (2017). Incidence and severity of self-reported chemotherapy side effects in routine care: A prospective cohort study. PloS one, 12(10), e0184360.

Sørensen, B., & Ingerslev, J. (2012). Dynamic APTT parameters: applications in thrombophilia. Journal of Thrombosis and Haemostasis, 10(2), 244-250.

Tsang, C. M., Yip, Y. L., Lo, K. W., Deng, W., To, K. F., Hau, P. M., . . . Lung, M. L. (2012). Cyclin D1 overexpression supports stable EBV infection in nasopharyngeal epithelial cells. Proceedings of the National Academy of Sciences, 109(50), E3473-E3482.

Waller, A. V. (1850). XX. Experiments on the section of the glossopharyngeal and hypoglossal nerves of the frog, and observations of the alterations produced thereby in the structure of their primitive fibres. Philosophical Transactions of the Royal Society of London(140), 423-429.

Zheng, H., Chen, C., Zhang, J., & Hu, Z. (2016). Mechanism and therapy of brain edema after intracerebral hemorrhage. Cerebrovascular diseases, 42(3-4), 155-169.