Primary Pituitary EBV-associated NK/T-cell Lymphoma

Stefan Motov (stefanmotov@yahoo.de)
Universitätsklinikum Augsburg: Universitatsklinikum Augsburg

Vicki Marie Butenschoen
Klinikum rechts der Isar der Technischen Universität München: Klinikum rechts der Isar der Technischen Universitat Munchen

Yu-Mi Ryang
HELIOS Klinikum Berlin-Buch

Jens Gempt
Klinikum rechts der Isar der Technischen Universität München: Klinikum rechts der Isar der Technischen Universitat Munchen

Tobias Boeckh-Behrens
Klinikum rechts der Isar der Technischen Universität München: Klinikum rechts der Isar der Technischen Universitat Munchen

Friederike Liesche-Starnecker
Klinikum rechts der Isar der Technischen Universität München: Klinikum rechts der Isar der Technischen Universitat Munchen

Folker Schneller
Klinikum rechts der Isar der Technischen Universität München: Klinikum rechts der Isar der Technischen Universitat Munchen

Veit Rothhammer
Universitätsklinikum Erlangen: Universitatsklinikum Erlangen

Christian Seifert
Klinikum rechts der Isar der Technischen Universität München: Klinikum rechts der Isar der Technischen Universitat Munchen

Julia Slotta-Huspenina
Klinikum rechts der Isar der Technischen Universität München: Klinikum rechts der Isar der Technischen Universitat Munchen

---

Research Article

Keywords: EBV-positive, lymphoma, pituitary, extranasal NK-/T-cell, CNS

Posted Date: June 4th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-232367/v1

Abstract

Background

Primary pituitary NK-/T-cell lymphomas are extremely rare pathologies and there is only limited information about their clinical course, treatment and prognosis.

Case presentation

We present a case of a 78-year-old patient with a sellar nodular mass. After onset of symptoms with productive cough, hoarseness, swallowing disorder and recurrent fever her condition rapidly deteriorated. Open biopsy through a right pterional approach was performed and histopathological evaluation revealed an EBV-associated NK/ T-cell lymphoma. High-dose corticosteroid therapy was initiated. However the patient passed away 37 days after admission due to respiratory insufficiency.

Conclusion

We describe an unusual case of EBV-associated NK-/T-cell lymphoma of the CNS manifesting as a pituitary gland tumor. This particular entity presented with a pronounced aggressive local tumor growth with lethal outcome.

Background

Primary central nervous system lymphoma (PCNSL) represents almost 4 % of newly diagnosed central nervous system (CNS) tumors and is usually of the B-cell-phenotype classified as diffuse large B-cell lymphoma. PCNSL is an aggressive and rare type of non-Hodgkin lymphoma involving brain, spinal cord and the meninges [17]. Primary pituitary lymphoma, especially of the natural killer (NK)-/T-cell phenotype is extremely rare and there is limited information about clinical features, treatment and prognosis.

Case Presentation

A 78-years-old lady presented with productive cough, hoarseness, swallowing impairment, and recurrent episodes of fever (40° C; 104° F), which started 1 month prior to hospitalization. There were no further B symptoms like night sweats or weight loss. Past medical history was unremarkable except for mild hypothyroidism and recent hospitalization for syncope two weeks prior to admission. A cranial computed tomography (CT) scan had been performed in a primary care hospital two weeks prior to admission, which retrospectively revealed a nodular mass in the middle cranial fossa restricted to the sellar region. An empiric antibiotic treatment with ceftriaxone and metronidazole was previously initiated due to elevated serum inflammation markers without significant improvement. Clinical examination on admission revealed left-sided glossopharyngeal and recurrence nerve palsies.

Cranial magnetic resonance imaging (MRI) revealed a contrast enhancing (CE) solid mass in the sellar region with both-sided signal alterations of the optic tract beneath the optic chiasm (Figure 1 A) as well

as a CE lesion in the left jugular foramen (Figure 1 B) on T1-weighted imaging. Spinal MRI with CE did not show any further dissemination. CT of thorax, abdomen and pelvis with CE was unremarkable except for a left-sided kidney cyst. Electroencephalography (EEG) revealed a poorly modulated alpha rhythm without epileptogenic potentials.

Pituitary function tests on admission indicated a reduced cortisol serum level (0.7 µg/dl; ref: 10-25 µg/dl) and moderately elevated prolactine levels (178 ng/ml; ref: <23 ng/ml). The patient was substituted with hydrocortisone. Differential blood counts were normal. Except for an elevated lactate dehydrogenase (404 U/l) and a slightly elevated C-reactive protein (CRP) of 5,5 mg/dl, the routine laboratory results were normal. Diagnostic cerebrospinal fluid (CSF) puncture showed mixed pleocytosis with increased lymphocytic cell count (170 cells/µl), but no atypical cells were found. Elevated Epstein-Barr virus (EBV) counts ($2{,}1 \times 10^5$ Geq/ml) were detected by polymerase chain reaction (PCR) of CSF, however serologic markers did not indicate a manifest EBV infection (negative EBNA-1 IgG and VCA IgM). Herpes simplex virus (HSV) and human immunodeficiency virus (HIV) serologies were also negative.

During further course of treatment, the patient developed elevated sodium levels (165 mmol/l) with high urine output and osmolality (339 mosmol/k). However, sodium serum level did not normalize until we started desmopressin medication indicating a diabetes insipidus. Antibiotic and antiviral treatment with ceftriaxone/ampicillin and ganciclovir was initiated on day 6 after admission. Due to sustained elevated inflammation markers antibiotic treatment was escalated with piperacillin/tazobactam on day 12. An episode with respiratory insufficiency due to glossopharyngeal nerve palsy occurred on day 13 and the patient was intubated and transferred to the intensive care unit. Once again antibiotic treatment was escalated with meropenem due to suspected urosepsis caused by vancomycin resistant enterococcus faecalis. Microbiological CSF cultures were negative for bacterial or fungal infection so ceftriaxone and ganciclovir were discontinued.

On day 19 an open tumor biopsy was performed through a right-sided pterional craniotomy with optic nerve decompression. Histopathological evaluation revealed a diffuse infiltrate of medium-sized to large lymphoid cells with irregular folded nuclei, granular chromatin, small nucleoli and a narrow to moderate rim of pale to clear cytoplasm (Figure 3A, hematoxylin/eosin, 400x). Mitotic figures were readily found. There was some geographic necrosis and angiocentric growth. By immunohistochemistry, the lymphoid cells stained positive for the T-cell markers CD2 and CD3 (Figure 3B), the NK-cell marker CD56 (Figure 3C) and the cytotoxic marker granzyme B (Figure 3D), whereas CD20 (Figure 3F), CD138 and Mum1 were negative. The proliferative fraction, as demonstrated by Ki-67 immunostaining was > 90 %. EBV in situ hybridisation was strongly positive in the tumor cells (Figure 3E) and the diagnosis of an EBV-associated lymphoma of the NK/T-cell phenotype was made. Due to limited tissue, neither further immunohistochemical stainings nor molecular studies could be performed.

On day 26 a left-sided hygroma, which was detected on postoperative imaging (Figure 2A), was evacuated through a frontal burr hole in local anaesthesia. Cranial MRI +/- CE additionally indicated growing lesions in the sellar and suprasellar region with compression of the optic chiasm (Figure 2A) and

progressive lesions at the right-sided oculomotor nerve (Figure 2C). The tumor mass in the jugular foramen also progressed over time (Figure 2B,C). A dilative tracheotomy was performed since the patient developed ongoing aspiration due to glossopharyngeal palsy. After tapering sedation, we noticed a new right-sided oculomotor palsy. Due to a reduced state of consciousness, we were not able to examine visual acuity and visual fields throughout treatment.

Ultimately therapy with dexamethasone 40 mg daily was initiated and the patient was transferred to the oncologic department for further treatment. Despite corticosteroid medication, her status deteriorated rapidly preventing additional diagnostics and chemotherapy. The patient died due to respiratory insufficiency 37 days after admission.

Discussion

Primary pituitary lymphoma (PPL) is an extremely rare subtype of PCNSL [14]. Common sellar tumor lesions are pituitary adenomas, craniopharyngiomas, Rathke's cleft cysts, meningiomas, germ cell tumors and carcinoma metastases [2,3,15]. A metaanalysis of 802 publications systematically reviewing literature up to October 2015 [15] described only 33 cases of PPL. In previous reported cases 82 % (27 cases) were B-cell lymphomas, 15 % (5 cases) were T-cell lymphomas and only one case was a NK/T-cell lymphoma (3 %) [8,15]. Extranodal NK/T-cell lymphoma is an aggressive lymphoma, which classically involves the nasal cavitiy and the aerodigestive tract and frequently extends locoregionally to the paranasal sinuses, orbits and lymph nodes. Sporadically it develops in non-nasal areas (skin, gastrointestinal tract, testis, soft tissue) as extranasal NK/T-cell lymphoma or as disseminated disease with a leukemic phase [4,16]. It has been suggested that most cases of extranasal NK/T-cell lymphoma actually have dissseminated occult nasal lymphoma [5,13]. Furthermore EBV appears to play an important etiologic role in the genesis as the virus has been detected in almost all cases [4,7]. Though NK/T-cell lymphoma has been related to EBV, evidence for a viral/tumor relationship is limited and the mechanisms of EBV entry into NK cells remain uncertain [7]. In fact EBV-genome is frequently positive in PCNSL cells in immunocompromised patients as an EBV infection is related to the transformation of normal lymphocytes. A chronic inflammation or a previous hypophysitis have also been suspected to induce a clonal transformation in lymphoma [9]. Moreover the coexistence of pituitary adenoma may predispose the secondary development of pituitary lymphoma, since pituitary hormones like prolactin might enhance mitosis in normal lymphoid cells and lymphatic tissue cells possess hormonal receptors [12,10]. However there was no evidence for an underlying pituitary adenoma in this case. Based on morphology, immunophenotype (expression of the T-cell markers CD2/CD3, CD56 and granzyme B) and the presence of EBV encoded RNA (EBER) by in-situ hybridisation the diagnosis of an extranodal EBV-positive NK/T-cell lymphoma was established. Interestingly radiological findings did not reveal any tumor manifestations beyond the CNS as there were no lesions involving the nasal or paranasal sinuses, nor the aerodigestive tract. However a minor tumor manifestation outside the CNS cannot be excluded, since a F18-florodeoxyglucose (FDG) positron emission tomography (PET)-CT, which is a mandatory initial diagnostic imaging [16], was not performed. On the other hand plasma EBV DNA level, which is a reliable diagnostic and prognostic surrogate [6,16], was low indicating low lymphoma load. Even if extranodal

NK/T-cell lymphoma frequently presents as limited early-stage disease it frequently disseminates with a rare CNS involvement and a median survival of 20 months across groups (7 years for early-stage I compared with only 7 months for stage IV) [11,1]. Chemotherapy and consolidation radiotherapy are usually the main treatment in extranodal NK/T-cell lymphoma, but response rates especially in advanced-stage disease remain poor and overall survival is limited [11,15]. In relapsed/refractory cases, blockade of the programmed death protein 1 (PD1) has recently shown promising results with high response rates [16]. Targeted therapies based on CD30/38 tumor cell expression also demonstrated beneficial results in ongoing studies [1]. A secondary analysis of a phase III trial in PCNSL demonstrated a longer overall survival and progression free survival in patients undergoing subtotal or gross total resection compared to those undergoing biopsy only [18]. We aimed a debulking surgery in our patient since intracranial dissemination and poor general condition prevented a gross total resection. Further tumor growth impeded chemotherapy and led to an unfavourable outcome.

Conclusion

To the best of our knowledge we describe the second case of a primary pituitary EBV-associated NK-/T-cell lymphoma, which compared to other PCNSL appears to have a highly aggressive and rapid tumor growth with fatal outcome. Further investigations might benefit to find out the specific role of EBV infection in the activation of NK/T-cells and the particular involvement of pituitary cells as possible therapy targets.

Declarations

Ethics approval and consent to participate

The research conducted has been performed in accordance with the Declaration of Helsinki. Due to the case report nature of our manuscript no ethics approval was considered neccessary.

Consent for publication

The husband of the patient gave written informed consent for publication of his wife's personal and clinical details along with any identifying images in this study. All authors read and approved the final manuscript.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this publication.

Funding

No funding to declare.

Authors' contributions

SM, VB, YR, JG, TBB, FL, FS, VR, CS, JSH made substantial contributions to conception and design, or acquisition of data, analysis and interpretation of data; SM and JSH have been involved in drafting the manuscript and revising it critically for important intellectual content; JSH has given final approval of the version to be published. JSH and FL supplied the histopathological images, TBB commented on the MRI/CT imaging and VB, YR, JG, VR and CS critically revised the clinical data; SM and JSH agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements

None.

References

1. Allen PB, Lechowicz MJ (2019) Management of NK/T-Cell Lymphoma, Nasal Type. J Oncol Pract 15:513-520. doi:10.1200/JOP.18.00719
2. Famini P, Maya MM, Melmed S (2011) Pituitary magnetic resonance imaging for sellar and parasellar masses: ten-year experience in 2598 patients. J Clin Endocrinol Metab 96:1633-1641. doi:10.1210/jc.2011-0168
3. Giustina A, Gola M, Doga M, Rosei EA (2001) Clinical review 136: Primary lymphoma of the pituitary: an emerging clinical entity. J Clin Endocrinol Metab 86:4567-4575. doi:10.1210/jcem.86.10.7909
4. Haverkos BM, Pan Z, Gru AA, Freud AG, Rabinovitch R, Xu-Welliver M, Otto B, Barrionuevo C, Baiocchi RA, Rochford R, Porcu P (2016) Extranodal NK/T Cell Lymphoma, Nasal Type (ENKTL-NT): An Update on Epidemiology, Clinical Presentation, and Natural History in North American and European Cases. Curr Hematol Malig Rep 11:514-527. doi:10.1007/s11899-016-0355-9
5. Jhuang JY, Chang ST, Weng SF, Pan ST, Chu PY, Hsieh PP, Wei CH, Chou SC, Koo CL, Chen CJ, Hsu JD, Chuang SS (2015) Extranodal natural killer/T-cell lymphoma, nasal type in Taiwan: a relatively

higher frequency of T-cell lineage and poor survival for extranasal tumors. Hum Pathol 46:313-321. doi:10.1016/j.humpath.2014.11.008

6. Kim HS, Kim KH, Kim KH, Chang MH, Ji SH, Lim DH, Kim K, Kim SJ, Ko Y, Ki CS, Jo SJ, Lee JW, Kim WS (2009) Whole blood Epstein-Barr virus DNA load as a diagnostic and prognostic surrogate: extranodal natural killer/T-cell lymphoma. Leuk Lymphoma 50:757-763. doi:10.1080/10428190902803669
7. Lee JH, Choi J, Ahn YO, Kim TM, Heo DS (2018) CD21-independent Epstein-Barr virus entry into NK cells. Cell Immunol 327:21-25. doi:10.1016/j.cellimm.2018.01.011
8. Liu JK, Sayama C, Chin SS, Couldwell WT (2007) Extranodal NK/T-cell lymphoma presenting as a pituitary mass. Case report and review of the literature. J Neurosurg 107:660-665. doi:10.3171/JNS-07/09/0660
9. Mathiasen RA, Jarrahy R, Cha ST, Kovacs K, Herman VS, Ginsberg E, Shahinian HK (2000) Pituitary lymphoma: a case report and literature review. Pituitary 2:283-287. doi:10.1023/a:1009969417380
10. Murakami Y, Sato T, Jinguji S, Kishida Y, Watanabe T, Suzuki O, Ikeda K, Homma M, Midorikawa S, Saito K (2016) [Primary Pituitary Malignant Lymphoma that was Difficult to Differentiate from Nonfunctioning Pituitary Adenoma:A Case Report]. No Shinkei Geka 44:779-784. doi:10.11477/mf.1436203376
11. Nevel KS, Pentsova E, Daras M (2019) Clinical presentation, treatment, and outcomes of patients with central nervous system involvement in extranodal natural killer/T-cell lymphoma. Leuk Lymphoma 60:1677-1684. doi:10.1080/10428194.2018.1551541
12. O'Neal KD, Schwarz LA, Yu-Lee LY (1991) Prolactin receptor gene expression in lymphoid cells. Mol Cell Endocrinol 82:127-135. doi:10.1016/0303-7207(91)90023-l
13. Shet T, Suryawanshi P, Epari S, Sengar M, Rangarajan V, Menon H, Laskar S (2014) Extranodal natural killer/T cell lymphomas with extranasal disease in non-endemic regions are disseminated or have nasal primary: a study of 84 cases from India. Leuk Lymphoma 55:2748-2753. doi:10.3109/10428194.2014.894188
14. Shin DW, Kim JH, Kim YH, Cho YH, Hong SH (2020) Primary central nervous system lymphoma involving the hypothalamic-pituitary axis: a case series and pooled analysis. J Neurooncol 147:339-349. doi:10.1007/s11060-020-03422-x
15. Tarabay A, Cossu G, Berhouma M, Levivier M, Daniel RT, Messerer M (2016) Primary pituitary lymphoma: an update of the literature. J Neurooncol 130:383-395. doi:10.1007/s11060-016-2249-z
16. Tse E, Kwong YL (2016) Diagnosis and management of extranodal NK/T cell lymphoma nasal type. Expert Rev Hematol 9:861-871. doi:10.1080/17474086.2016.1206465
17. Villano JL, Koshy M, Shaikh H, Dolecek TA, McCarthy BJ (2011) Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. Br J Cancer 105:1414-1418. doi:10.1038/bjc.2011.357
18. Weller M, Martus P, Roth P, Thiel E, Korfel A, German PSG (2012) Surgery for primary CNS lymphoma? Challenging a paradigm. Neuro Oncol 14:1481-1484. doi:10.1093/neuonc/nos159

Figures

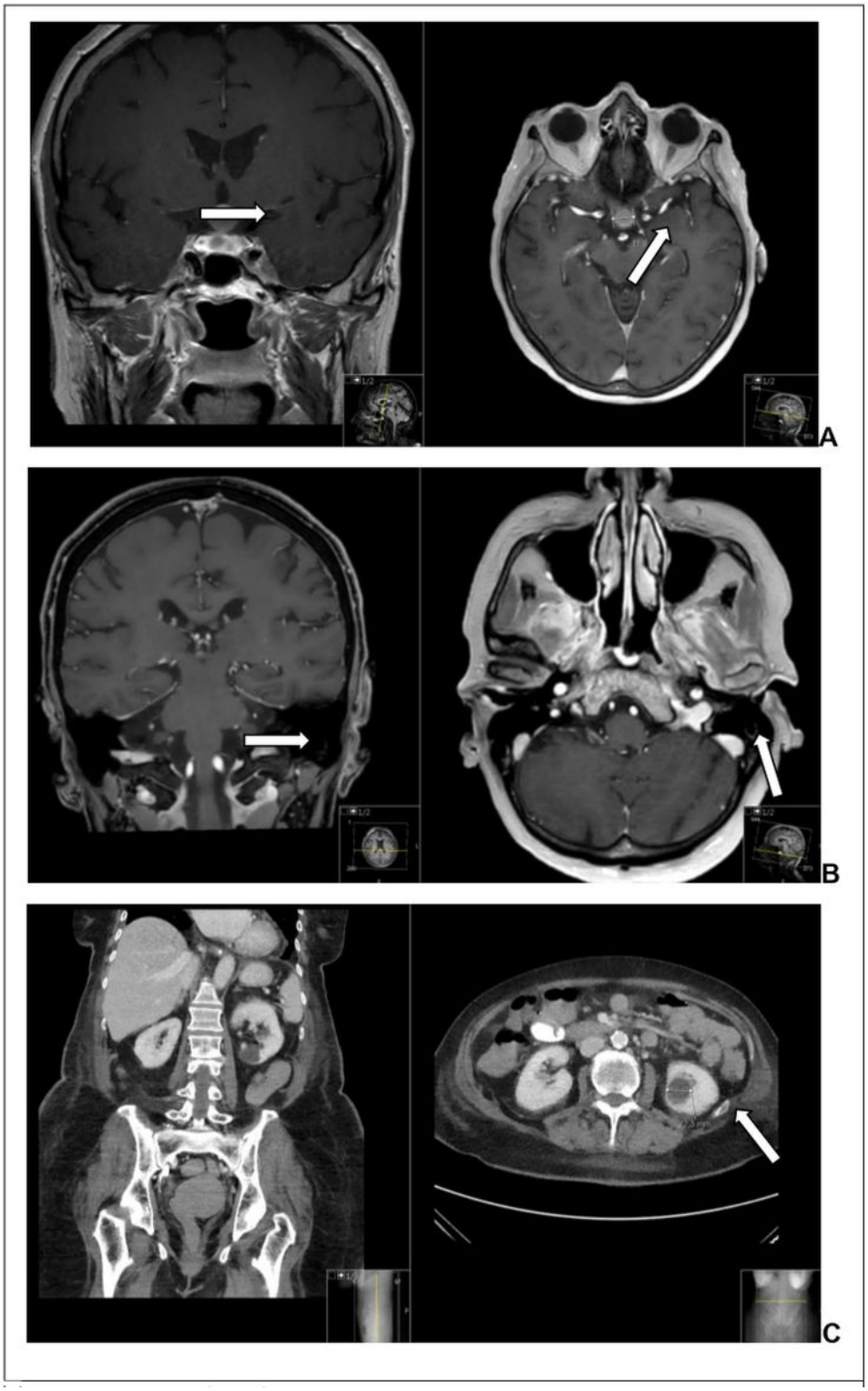

Figure 1

Preoperative Imaging

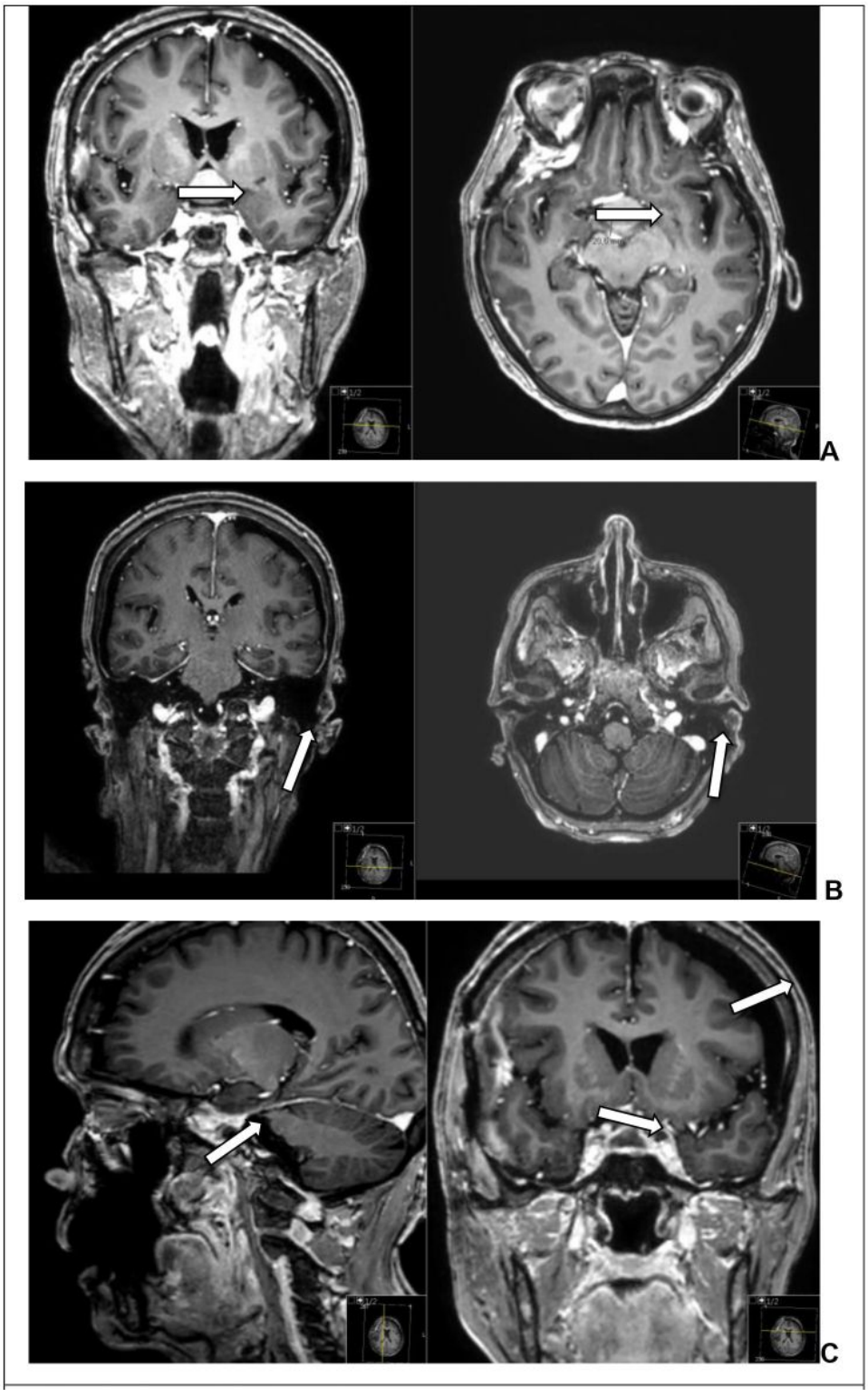

Figure 2

Postoperative Imaging

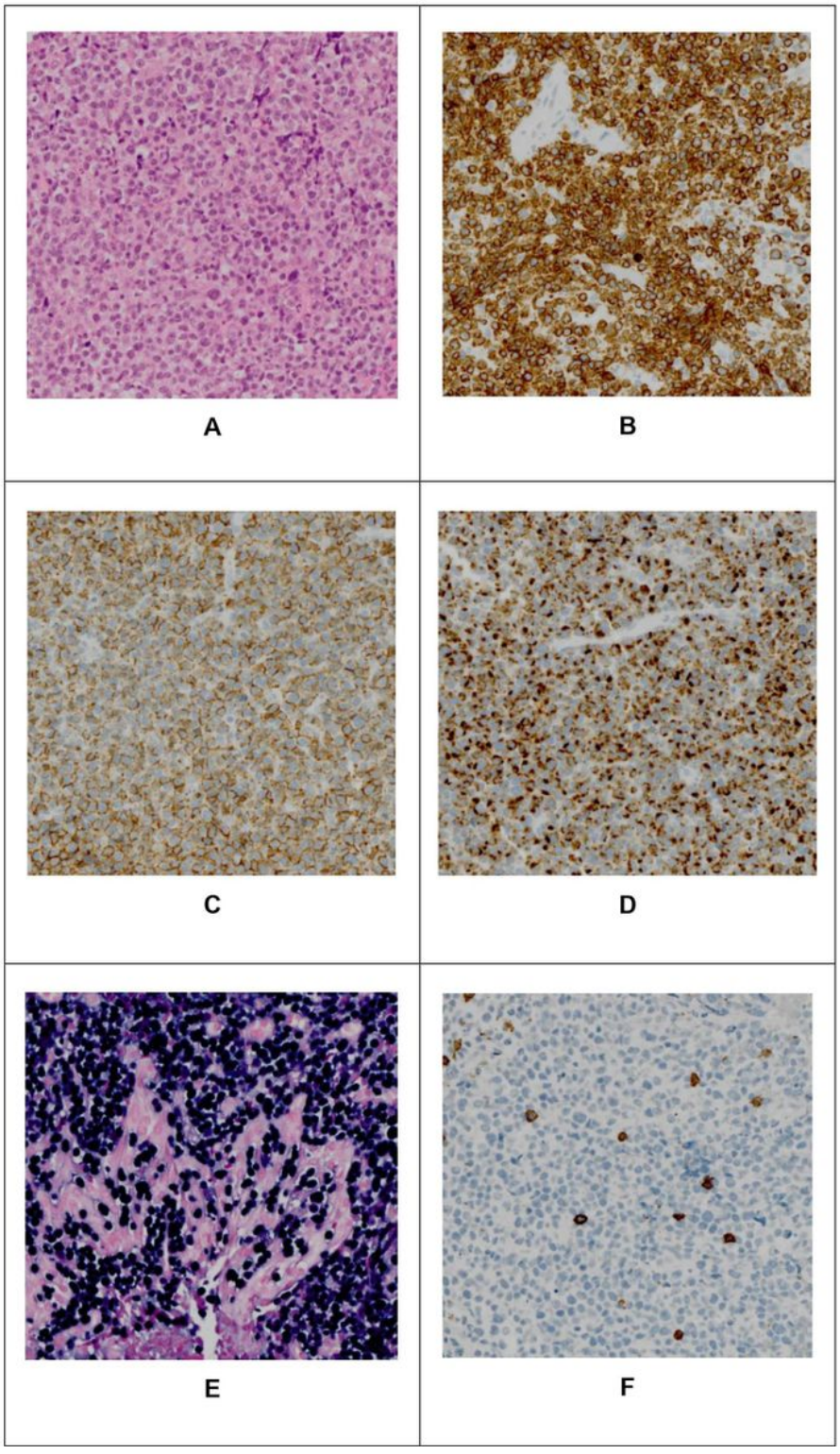

Figure 3

Histopathology (200x magnification)