Pituitary Gland as a Rare Primary Localization of Lymphoma

Nadir Bir Primer Lenfoma Lokalizasyonu: Hipofiz Bezi

Burak ÖZBAŞ, Özlem CANÖZ*, Zeynep GÜVEN**, İzzet ÖKÇESİZ***, Hüseyin DURSUN, Ahmet SELÇUKLU****, Hatice YILMAZ*****
Züleyha KARACA, Kürşad ÜNLÜHIZARCI

Division of Endocrinology and Metabolism, Erciyes University Faculty of Medicine, Kayseri, TURKIYE
*Department of Pathology, Erciyes University Faculty of Medicine, Kayseri, TURKIYE
**Department of Hematology, Erciyes University Faculty of Medicine, Kayseri, TURKIYE
***Department of Radiology, Erciyes University Faculty of Medicine, Kayseri, TURKIYE
****Department of Neurosurgery, Erciyes University Faculty of Medicine, Kayseri, TURKIYE
*****Department of Internal Medicine, Erciyes University Faculty of Medicine, Kayseri, TURKIYE

Keywords: Pituitary tumor; lymphoma; diplopia; headache; visual loss

Abstract
Lymphomas are the rare causes in the differential diagnosis of pituitary masses. While pituitary infiltration by lymphomas is relatively more frequent, isolated lymphoma associated with the pituitary gland is much rarer. We presented a case of a 64-year-old female patient who was admitted to the hospital due to headache, diplopia and decreased visual acuity. Although the stated preoperative diagnosis was parasellar meningioma, the pathological diagnosis was given as isolated primary pituitary lymphoma after ruling out any other foci. After the definitive diagnosis, the patient underwent chemoradiotherapy. However, despite treatment, the patient died due to pulmonary sepsis. Primary pituitary lymphoma is an extremely rare condition generally seen in elderly and/or immunosuppressive patients. In order to establish an effective therapeutic strategy, it is extremely crucial to distinguish between primary and secondary lymphomas. However, the recent evidence for a standardized treatment protocol is still limited due to the small number of cases reported to date.

Özet
Lenfomalar, son derece nadir görülmektedir, hipofiz kitlelerinin ayrıncı olarak ngạiされます. Lenfomaların pitüütler infiltrasyonları genellikle daha sık karşılaşılmakla birlikte, hipofiz bezinin izole primer lenfoması çok daha nadirdir. Bu olguda, hastaneye baş ağrısı, çift görme ve görme keskinliğinin azalması, 64 yaşında bir kadının hastalığından teşhis edilmişdir. Preoperatif tanı parasellar menenjöma olan hastaya, vücutta herhangi bir ek odak olmadığı gösterilmesi arından izole primer pitüütler lenfoması tanısı konuldu. Tanınakın kesinleşmesinin ardından hastaya kemoterapi başlanmıştır. Kemoterapi ve radyoterapiin hızla başlanması karınsha hatta, tedavini 3. ayında akciğer enfeksiyonuna sekonder sepsis nedeniyle kaybedildi. Pitüütler lenfomaların son derece nadir olup, ileri yaşta ve/veya immünsuprese hastalarda daha sık görülmektedir. Primer ve sekonder lenfomaların ayrıncı tanının yapılması, etkin bir tedavi belirlemek için çok önemlidir. Ancak günümüzde raporlanmış oğulların az sayıda olması nedeniley standardize bir tedavi protokolü için henüz yeterli kant bulunmamaktadır.

Keywords: Pituitary tumor; lymphoma; diplopia; headache; visual loss

Anahtar kelimeler: Pitüütler tümör; lenfoma; diplopi; baş ağrısı; görme kaybı

Address for Correspondence: Kürşad ÜNLÜHIZARCI, Division of Endocrinology and Metabolism, Erciyes University Faculty of Medicine, Kayseri, TURKIYE
Phone: +90 352 207 66 66 E-mail: kursad@erciyes.edu.tr

Peer review under responsibility of Turkish Journal of Endocrinology and Metabolism.

Received: 18 Jun 2021 Received in revised form: 11 Nov 2021 Accepted: 07 Dec 2021 Available online: 22 Dec 2021

DOI: 10.25179/tjem.2021-84943
Introduction

The pituitary gland is one of the most common localization of intracranial tumors as well as a rare manifestation of systemic malignancy that can be life-threatening. More frequent use of both superior imaging methods and endocrine tests has now led to an increasing number of pituitary masses being diagnosed on time. Although most of the detected masses are adenomas (90%), other lesions can also be found in the pituitary gland (1), like the lesions in sellar and parasellar regions that include craniopharyngiomas, meningiomas, gliomas, granulomas, germ cell tumors and metastatic cancers. Both solid and hematologic malignancies can metastasize to the pituitary gland resulting in a poor prognosis in some cases. The most common solid cancers that usually metastasize to the pituitary gland are lung (31%), breast (26.2%), and kidney (8.1%) malignancies. Hematological malignancies also localize in the pituitary gland either primarily or as a secondary manifestation of the primary disease (2). On the one hand, primary central nervous system lymphoma (PCNSL) is one of the primary malignancies that can cause metastasis and nearly accounts for 2.3% of the mass lesions in the brain and central nervous system (CNS), the frequency of this disease has been increased in the last 2 decades (3). On the other hand, primary pituitary lymphoma (PPL) is an extremely rare pathology, which was first reported in an immunocompromised patient, and later was detected in several patients without a known immunosuppressive state (4). As PPL is extremely difficult to diagnose by the radiological or laboratory methods in the preoperative period, the definitive diagnosis can only be achieved by precise postoperative histopathological evaluation to maintain accuracy. Therefore, in this paper, we described a case of PPL who was admitted to the hospital because of headache and diplopia.

Case Report

A 64-year-old woman without any chronic disease presented with headache, diplopia and a decrease in visual acuity for the past 3 months. Further, magnetic resonance imaging (MRI) of the sellar region revealed an isolated sellar mass extending to the suprasellar cistern on the left side of the pituitary gland. The lesion exhibited contact with the optic chiasm besides showing invasion in the left cavernous sinus (Figure 1.1, Figure 1.2).

Laboratory findings did not show either hyper or hypofunction of the pituitary gland (Table 1). Complete blood count and serum biochemistry were within the normal limits. The patient underwent transsphenoidal surgery with a preoperative diagnosis of parasellar meningioma. However, since the mass could not be completely removed due to its hard and adherent nature, only a biopsy was taken, and the surgical procedure was terminated. Histopathological examination of the surgical specimen revealed a diffuse proliferation of atypical cells with areas of perivascular growth. The tumor cells showed positive immunocytochemistry with CD20 (diffuse expression), MUM1 and BCL-6, but CD10, CD5, and BCL-2 expressions were found to be negative (Figure 2).
Moreover, fluorescence in situ hybridization results for Epstein-Barr virus-encoded small RNAs were also negative. Based on these pathological and immunohistochemical findings, a diagnosis of diffuse large B-cell lymphoma was established. Since positron emission tomography-computed tomography (PET-CT) examination did not reveal any pathological 18F-fluorodeoxyglucose (FDG) uptake in the body (including pituitary) while lumbar puncture and bone marrow biopsy revealed the absence of infiltration in the whole body, the definitive diagnosis of PPL was made. After the development of polyuria and polydipsia as a result of pituitary surgery, the patient was diagnosed with central diabetes insipidus (DI), and intranasal vasopressin therapy was started. After the definitive diagnosis of PPL, since radiotherapy was planned as the first-line treatment due to frequent headaches experienced by the patient, a dose of 3,600 cGy was administered in 22 fractions of 180 cGy in 22 days by stereotactic body radiation therapy. Furthermore, an intensive chemotherapy protocol, the methotrexate,

|                        | Normal range       | Normal range       |
|------------------------|--------------------|--------------------|
| Prolactin (ng/mL)      | 19.5               | 1.8-20.3           |
| IGF-1 (ng/mL)          | 167                | 51-187             |
| FSH (mIU/mL)           | 21.04              | 23-116             |
| LH (mIU/mL)            | 12.4               | 23-116             |
| Estradiol (pg/mL)      | 41.41              | 5-138              |
| Free T3 (pg/mL)        | 2.86               | 2-4.4              |
| Free T4 (ng/dL)        | 1.21               | 0.91-1.97          |
| TSH (µIU/mL)           | 0.88               | 0.27-4.2           |
| Cortisol (µg/dL)       | 12.8               | 6.2-18             |
| ACTH (pg/mL)           | 17.8               | 0-46               |
| Hemoglobin (g/dL)      | 15.3               | 12-16              |
| Hematocrit (%)         | 47.5               | 37-47              |
| Leukocyte 10^9/µL      | 7.7                | 4.8-10.7           |
| Platelet count 10^9/µL | 354                | 150-400            |
| ESR (mm/h)             | 15                 | 0-20               |

IGF-1: Insulin-like growth factor 1; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid-stimulating hormone; ACTH: Adrenocorticotropic hormone; ESR: Erythrocyte sedimentation rate; BUN: Blood urea nitrogen; AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma-glutamyltransferase; CRP: C-reactive protein.
cytarabine, thiopeta, and rituximab regimen (MATRix), was applied. The protocol was as follows: methotrexate 3.5 g/m² on day 1, cytarabine 2 g/m² twice daily on days 2 and 3, 2 doses of 375 mg/m² rituximab on days 5 and 0, as well as 30 mg/m² thiopeta on day 4. As the general condition of the profoundly neutropenic patient deteriorated on the 20th day of chemotherapy, the patient died due to pneumosepsis.

Consent form could not be obtained due to the death of the patient.

Discussion

This paper presented a rare and unusual case of PPL with only 40 immunocompetent cases identified and reported to date in the entire literature (5). Although PPL is an intracranial lesion, these lesions have different embryological origins than the usual CNS origin. However, since there are very few PPL cases reported in the literature, PCNSL guidelines are utilized in the treatment of this disease (6).

Although Tarabay et al. in 2016 observed a slight female predominance in the distribution of cases (female: male ratio 1.35:1), this difference was not seen in the recent studies (female: male ratio 1:1 and 1.12:1, respectively). Moreover, it can appear in all age groups, with a peak incidence observed between the 5th and the 6th decade of life (5-7). Pituitary lymphoma can be either primary or secondary. The differential diagnosis of primary/secondary pituitary lymphoma is essential to determine the stage of the disease as well as to select an appropriate treatment modality. In order to make an accurate, definitive diagnosis, several investigative procedures like PET-CT, bone marrow biopsy, and lumbar puncture should be duly incorporated in the patients’ diagnostic protocol.

Although several theories exist, the etiology for PPL or PCNSLs is still ambiguous. The most important risk factor is the presence of the immunodeficiency state in the body, as the first reported PPL case was described in a patient with AIDS (4). However, the occurrence of this disease in patients without any known immunodeficiency suggests that it might be related to different etiologies. Firstly, the tumor might arise either from CNS lymphoid tissue or from neoplastic transformation of lymphocytes that migrate to the CNS following an inflammatory phase (8). Furthermore, the application of radiotherapy to the skull or a history of chemotherapy for a brain tumor was also stated as an important risk factor (6). It has also been suggested that the Epstein-Barr virus, which is a common triggering component for lymphomas, might be a potential risk factor. In our case report, the viral serology examination was negative for Epstein-Barr virus infection, while a positive Epstein-Barr virus result was found in only one case in the current literature database (9).

Another theory regarding the PPL origin is that it may develop as a secondary manifestation of lymphocytic hypophysitis or pituitary adenoma (10). Although few case reports support the above-mentioned theories (9,11), no signs of lymphocytic hypophysitis or adenoma were detected in the histopathological examination in the present case.

The clinical findings of PPL might be similar to the observations seen in pituitary adenomas. Furthermore, B symptoms (fever, night sweats, weight loss) that are seen in systemic lymphomas, are absent in both PCNSL and PPL at the time of diagnosis (12). Patients may have complaints of headache, diplopia, cranial nerve paralysis, fatigue, nausea, vomiting and retroorbital pain (6).

The various neurological symptoms observed in PPL are directly proportional to the location of the mass. Since visual defects along with pituitary dysfunction are common in suprasellar and intrasellar masses, neither anterior nor posterior pituitary dysfunction was detected at the time of diagnosis in our case. Anterior pituitary dysfunction is more commonly seen in primary tumors, while posterior pituitary dysfunction is more commonly observed in the metastatic lesions at the diagnostic stage (9,13). The early involvement of the posterior pituitary with metastatic lesions may be due to the fact that this region receives its vascular supply directly from the systemic circulation (13). Although the etiology of DI seen in our patient is unclear, it may be caused either by surgical trauma or as a secondary manifestation due to the progression of the primary disease. Since postoperative imaging methods could not be employed, it is not
feasible to mention the progression of the PPL or the associated edema secondary to radiotherapy. In a study by Tarabay et al, 36% of PPL patients were found to have DI (6).

Although they do not provide a definitive diagnosis, imaging methods help narrow the causes as well as predict the possible presence of the disease. MRI is frequently used in the differential diagnosis of pituitary masses, though sometimes due to the overlapping of the MRI findings of pituitary adenomas and PPL, the distinction between adenoma and PPL cannot be made definitively (14). The PPL symptoms might also cause confusion with the meningioma symptoms in the preoperative period (15), which were similar to the present case. Nevertheless, in elderly and immunocompromised patients, PPL should always be considered in the differential diagnosis of invasive sellar/parasellar lesions that have low to intermediate signal intensity on T1- and T2-weighted MRI images and, therefore, enhance avidly (16,17). Few nonspecific findings such as pituitary enlargement, suprasellar or cavernous sinus extension, and thickening of the stalk might be seen in PPL (9). Since pituitary adenomas sometimes appear as hypermetabolic masses, even FDG-PET scan cannot provide a definitive differential diagnosis (18).

PPL cannot be precisely identified in the preoperative period and can only be diagnosed with histopathological examination. Although the majority of PPL cases are of B lymphocyte origin (80%), natural killer and T cell lymphoma may also be present in some areas (7). A study observed that in some cases, it is also possible to encounter signs of inflammation or adenomatous tissue, which has also been mentioned above (10).

Due to the aggressive course of PCNSLs, early diagnosis and prompt treatment are very important. The current treatment approaches consist of surgery, radiotherapy, chemotherapy, and their combinations (5). Although it is stated that surgery does not provide a survival advantage in secondary pituitary involvement, but the issue of surgical intervention for PCNSL is controversial. Weller et al. reported that improved outcomes were obtained in PCNSL patients who underwent total or subtotal resection (2,12,19) whereas, in most cases of PPL, removal of the entire tumor mass is usually not possible (6). Although there is heterogeneity in the treatment protocol of patients evaluated retrospectively, chemotherapy regimens containing high-dose methotrexate have recently been demonstrated to provide a survival advantage (20,21). Additionally, the combination of chemotherapy, as well as radiotherapy, has also been proved to be beneficial in treating such cases (6,22).

To conclude, as PPL is a rare entity in clinical endocrinology practice, it should be duly considered in seeking the differential diagnosis in invasive sellar/parasellar masses, especially in elderly and/or immunocompromised patients. Although there is no specific treatment guideline due to the small number of cases, it should be considered that PPL has its unique properties and should be considered as a separate entity due to its placement outside the blood-brain barrier as well as the emergence of various adverse effects (both endocrinological and neurological) related to the treatment. Due to its rarity, PPL cases should be collected to gather factual evidence for better patient outcomes. Furthermore, molecular studies are also required in the near future to investigate the pathogenesis and explore new biomarkers for early detection and prompt therapeutic interventions.

Source of Finance
During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest
No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.
Authorship Contributions
Idea/Concept: Burak Özba; Design: Burak Özba; Control/Supervision: Kürşad Ünlühızarcı, Züleyha Karaca; Data Collection and/or Processing: Hüseyin Dursun, Ahmet Selçuklu, Hatice Yilmaz, Özlem Canöz, İzzet Ökçesiz; Analysis and/or Interpretation: Burak Özba, Özlem Canöz; Literature Review: Burak Özba; Writing the Article: Burak Özba, Özlem Canöz, Zeynep Güven, İzzet Ökçesiz; Critical Review: Kürşad Ünlühızarcı; References and Fundings: Burak Özba; Materials: Kürşad Ünlühızarcı, Ahmet Selçuklu, Özlem Canöz.

References
1. Clayton RN. Sporadic pituitary tumours: from epidemiology to use of databases. Baillieres Best Pract Res Clin Endocrinol Metab. 1999;13:451-460. [Crossref] [PubMed]
2. Ng S, Fenech N, Delabar V, Jacquesson T, Enache C, Raverot G, Manet R, Jouanneau E. Current status and treatment modalities in metastases to the pituitary: a systematic review. J Neurooncol. 2020;146:219-227. [Crossref] [PubMed]
3. Mufti ST, Baeesa SS, Al-Maghrabi JA. Primary intracranial lymphomas. Asian J Neurosurg. 2016;11:232-239. [Crossref] [PubMed] [PMC]
4. Gottfredsson M, Oury TD, Bernstein C, Carpenter C, Bartlett JA. Lymphoma of the pituitary gland: an unusual presentation of central nervous system lymphoma in AIDS. Am J Med. 1999;101:563-564. [Crossref] [PubMed]
5. Caputo M, Pencipe N, Bisceglia A, Bona C, Macyszyn G, Właszczyk E. Primary pituitary lymphoma in AIDS. Folia Neuropathol. 2012;20:1437-1440. [Crossref] [PubMed] [PMC]
6. Duan L, Liu J, Zhang Y, Cui L, Zhai X, Pan B, Lu L, Pan H, Yao Y, Zhu H. Primary pituitary lymphoma in immunocompetent patients: a report on two case studies and the review of literature. Front Endocrinol (Lausanne). 2021;11:562850. [Crossref] [PubMed] [PMC]
7. Rudnik A, Larysz D, Blamek S, Larysz P, Bierzyńska-Macyszyn G, Właszczyk P, Bazowski P. Primary pituitary lymphoma. Folia Neuropathol. 2007;45:144-148. [Crossref] [PubMed]
8. Liu JK, Sayama C, Chin SS, Couldwell WT. Extracranial NK/T-cell lymphoma presenting as a pituitary mass. Case report and review of the literature. J Neurosurg. 2007;107:660-665. [Crossref] [PubMed]
9. Giustina A, Gola M, Doga M, Rosci EA. Clinical review 136: Primary lymphoma of the pituitary: an emerging clinical entity. J Clin Endocrinol Metab. 2001;86:4567-4575. [Crossref] [PubMed]
10. Ban VS, Chaudhary BR, Allinson K, Santarius T, Kirrollos RW. Concomitant primary CNS lymphoma and FSH-pituitary adenoma arising within the sella. Entirely coincidental? Neurosurgery. 2017;80:E170-E175. [Crossref] [PubMed] [PMC]
11. Grommes C, DeAngelis LM. Primary CNS lymphoma. J Clin Oncol. 2017;35:2410-2418. [Crossref] [PubMed] [PMC]
12. Jaiswal PA, Nair P, Jacob PM, Abraham M, Gohil J. Metastatic pituitary lymphoma: Report and literature review. Neurol India. 2019;67:911-915. [PubMed]
13. Murakami Y, Sato T, Jingui S, Kishida Y, Watanabe T, Suzuki O, Ikeda K, Homma M, Midorikawa S, Saito K. [Primary pituitary malignant lymphoma that was difficult to differentiate from nonfunctioning pituitary adenoma:a case report]. No Shinkei Geka. 2016;44:779-784. Japanese. [PubMed]
14. Li J, Lei C, Richard SA, Liu Y. Giant solitary intracranial lymphoma masquerading as meningioma: a case and review of literature. Pan Afr Med J. 2017;28:196. [Crossref] [PubMed] [PMC]
15. Kaufmann TJ, Lopes MB, Laws JR Jr, Lipper MH. Primary solitary lymphoma: radiologic and pathologic findings in two patients. AJNR Am J Neuroradiol. 2002;23:364-367. [PubMed] [PMC]
16. Kaltsga GA, Kolomodi D, Randeva H, Grossman A. Nonneuroendocrine neoplasms of the pituitary region. J Clin Endocrinol Metab. 2019;104:3108-3123. [Crossref] [PubMed]
17. Shimon I. Metastatic spread to the pituitary. Neuroendocrinology. 2020;110:805-808. [Crossref] [PubMed]
18. Weller M, Martus P, Roth P, Thiel E, Korfel A. German PCNSL Study Group. Surgery for primary CNS lymphoma: Challenging a paradigm. Neuro Oncol. 2012;14:1481-1484. [Crossref] [PubMed] [PMC]
19. Gerstner ER, Carson KA, Grossman SA, Batchelor TT. Long-term outcome in PCNSL patients treated with high-dose methotrexate and deferred radiation. Neurology. 2008;70:401-402. [Crossref] [PubMed] [PMC]
20. Ferreri AJ, Cwynarski K, Pulszynski E, Ponzoni M, Deckert M, Politi LS, Torri V, Fox CP, Roséle PL, Schorb E, Ambrosetti A, Roth A, Hemmaway C, Ferrari A, Linton KM, Rudá R, Binder M, Pukrop T, Balzarotti M, Fabbri A, Johnson P, Gørløv JS, Hess G, Panse J, Pisani F, Tucci A, Stilgenbauer S, Hertenstein B, Keller U, Krause SW, Levis A, Schmoll HJ, Cavalli F, Finke J, Reni M, Zuccka E, Ilinerhaus G; International Extranodal Lymphoma Study Group (IELSG). Chemioimmunotherapy with methotrexate, cytarabine, thiopeta, and rituximab (MATTRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. Lancet Haematol. 2016;3:e217-e227. [Crossref] [PubMed]
21. Han CH, Batchelor TT. Diagnosis and management of primary central nervous system lymphoma. Cancer. 2017;123:4314-4324. [Crossref] [PubMed]