The sellar region as presenting theater for hematologic malignancies—A 17-year single-center experience

Sandra Pekic(1,2), Marko Stojanovic(1,2), Emilija Manojlovic Gacic(1,3), Darko Antic(1,4), Toplica Milojovic(5), Mihajlo Milicevic(1,5), Aleksandar Stanimirovic(5), Mirjana Dokić(1,2), Dragana Miljic(1,2), Sandra Banjalic(6), Marija Jovanovic(1,6), Zvezdana Jemiovic(2), Marina Nikolic Djurovic(1,2), Danica Grujicic(1,5), Vera Popovic(1) and Milan Petakov(1,2)

1) Medical Faculty, University of Belgrade, Belgrade, Serbia
2) Clinic for Endocrinology, Diabetes and Diseases of the Metabolism, University Clinical Center of Serbia, Belgrade, Serbia
3) Institute of Pathology, Belgrade, Serbia
4) Clinic for Hematology, University Clinical Center of Serbia, Belgrade, Serbia
5) Clinic for Neurosurgery, University Clinical Center of Serbia, Belgrade, Serbia
6) Center for Radiology and Magnetic Resonance Imaging, University Clinical Center of Serbia, Belgrade, Serbia

Abstract. Hematological neoplastic mass lesions of the sellar region are rare. We identified five cases of hematological malignancy with first presentation in the sellar region from our departmental database of 1,405 patients (0.36%) with sellar lesions diagnosed over the 17-year period (2005–2021). All patients were females (mean age 55.2 ± 3.4 years). One patient had multiple myeloma (MM), one patient had acute myeloid leukemia (AML), while three other patients had lymphoma (intravascular lymphoma (IVL, n = 1) or non-Hodgkin’s lymphoma (NHL, n = 2). Most patients presented with ophthalmoplegia, and one patient with diabetes insipidus (DI), with short duration of symptoms (median 30 days). All patients had an elevated erythrocyte sedimentation rate and altered blood count, while patients with lymphoma had elevated lactate dehydrogenase (LDH). Sellar mass was demonstrated in three patients while the patient with IVL had an empty sella and in the AML patient posterior lobe T1W hyperintensity was lost. Two patients (IVL and NHL) presented with multiple anterior pituitary deficiencies and one patient (AML) had DI. All patients were treated with chemotherapy. Two patients responded well to treatment (one had reversed hypopituitarism), while three patients died. Differential diagnosis of sellar-parasellar pathology should include suspicion of hematological malignancy, particularly in patients with short duration of nonspecific symptoms, neurological signs (ophthalmoplegia), blood count alterations and LDH elevation, pituitary dysfunction and imaging features atypical for pituitary adenoma. Early diagnosis is crucial for timely initiation of hematological treatment aimed at inducing disease remission and partial or full recovery of pituitary function.

Key words: Pituitary, Lymphoma, Leukemia, Multiple myeloma, Hypopituitarism
(five with diffuse large B-cell lymphoma and two with mucosa-associated lymphoid tissue (MALT) lymphoma [8].

Clinical presentations of pituitary hematological malignancies included headache, visual disturbances and ophthalmoplegia, as well as systemic non-specific symptoms (fatigue, weight loss, nausea, vomiting or perspiration). These symptoms usually appeared suddenly and worsened rapidly. Anterior pituitary deficiency and mild hyperprolactinemia due to compression of the pituitary stalk were frequent, while diabetes insipidus was rare. Current systemic medical therapy and radiotherapy for hematological malignancies are effective, and the prognosis of these malignancies in the sellar region is generally better in comparison with metastasis from solid cancers [5].

We present a case series of hematological malignancies in the sellar region, observed over a long period (17 years) in a tertiary care center with pituitary specialty, and in which pituitary infiltration was the initial presentation of a previously unsuspected hematological malignancy.

Patients and Methods

The patients with hematological malignancy in the sellar region were identified from our database of 1,405 patients with sellar and parasellar lesions diagnosed over a 17-year period (2005–2021) at the Department of Neuroendocrinology, tertiary care center with pituitary specialty, with endocrinologists, neurosurgeons, neuroradiologists and a neuropathologist specialized in the care of patients with sellar pathologies. Demographic data (gender and age at diagnosis), clinical presentation features (symptoms such as headache, cranial nerve palsies or visual field defects related to mass effect, or systemic symptoms), laboratory features (complete blood count, erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH) level), radiological findings (sellar radiography, sellar MRI), histological diagnosis, course of treatment (treatment protocol) and outcomes of hematologic malignancies were analyzed. Baseline serum hormone levels (cortisol, FT4, T4, TSH, FSH, LH, testosterone in males, estradiol in females, IGF-I and prolactin) were measured with commercial kits: FT4 by RIA (Cis BioInternational), T4 by radioimmunoassay (RIA, INEP, Serbia), TSH by immunoradiometric assay (IRMA, INEP, Serbia), prolactin by IRMA (Cis BioInternational), cortisol by RIA (Cis BioInternational), LH by IRMA (Cis BioInternational), FSH by IRMA (Cis BioInternational), GH by immunofluorimetric assay (Wallac-Turku, Finland), IGF-I by chemiluminescent enzyme immunoassay with the Immulite Analyzer (Diagnostic Product, Corporation, Los Angeles, CA, USA).

ACTH deficiency was diagnosed when serum cortisol level at 08:00 was <80 nmol/L, while in our patients with serious systemic illness, we applied the criteria of the American College of Critical Care Medicine, which advocates diagnosis of adrenal insufficiency in critically ill patients with random cortisol <276 nmol/L [9]. Secondary hypothyroidism was diagnosed when the thyroid hormone level (either fT4 or T4) was below the reference range with low or inappropriately normal TSH value. Secondary hypogonadism was confirmed when the LH and FSH concentrations were low or inappropriately normal with serum testosterone below the reference range in men, low or inappropriately normal with low serum estradiol in premenopausal women in the absence of regular menses or below the reference range for their age in post-menopausal women. Low-normal or low IGF-1 level (according to age-specific cut-offs) accompanied by more than three other hypothalamic-pituitary axis deficiencies indicated GH deficiency. Two stimulation tests, insulin tolerance test (ITT) and GH releasing hormone (GHRH), plus a GH-releasing peptide-6 (GHRP-6) test were performed in one patient for evaluation of the somatotroph axis (described in [10]). Central diabetes insipidus was diagnosed when hypotonic polyuria was associated with increased serum osmolality or serum sodium above the reference range. Magnetic resonance imaging (MRI) was performed at diagnosis and during the follow-up period. Chest and abdominal computed tomography (CT) and bone marrow biopsy were performed in all patients. Patients were treated with systemic chemotherapy, with or without radiotherapy and the primary outcome after treatment was described.

Statistical analysis

Continuous variables are expressed as the mean ± standard error or median (range). Categorical variables are expressed as numbers or percentages.

Results

Over the 17-year period, and out of 1,405 patients investigated for sellar/parasellar disorders, we identified five cases (0.36%) of sellar region lesions attributed to a previously undiagnosed hematological malignancy. All five patients were females. The mean age at diagnosis with hematological malignancy was 55.2 ± 3.4 years (range, 46 to 67 years, median 53 years). One patient had multiple myeloma (MM), one had acute myeloid leukemia (AML), while the other three had lymphoma (intravascular large B cell lymphoma (IVL, n = 1) or high-grade B cell non-Hodgkin’s lymphoma (NHL, n = 2 / in one patient in leukemic phase). The patients’ characteristics and diagnostic procedures are presented in detail.
**Patient 1**

A 53-year-old female presented with acute onset of diplopia, bitemporal hemianopia, malaise, perspiration, all evolving over 6 months. Physical examination revealed left-sided cranial nerve (CN) IV palsy, general lymphadenopathy and left-sided pleural effusion. On X-radiography, multiple skeletal lytic lesions were detected and the sellar region was enlarged and destructed (Fig. 1a). She had elevated ESR, anemia, thrombocytopenia and elevated LDH level (Table 1). On a sellar MRI, an invasive sellar tumor with symmetrical infiltration of both cavernous sinuses and the clivus were described (Fig. 1b–d). She had hypopituitarism and elevated prolactin level (Table 1). She was replaced with hydrocortisone (20 mg/d) and levothyroxine (100 μg/d). She was sent for transsphenoidal decompression. Tumor tissue was stained with hematoxylin-eosin for morphological evaluation. Hematological diagnosis of non-Hodgkin B follicular lymphoma was confirmed with immunohistochemistry (diffuse CD20, PAX5, bcl-2, bcl-6 and CD10 positivity) (Fig. 2).

The patient was transferred to the hematology department and was started on immunochemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone). After 6 months of therapy, her condition generally improved, she had no diplopia and her cranial nerve palsy normalized. Her MRI scan disclosed significant resolution of sellar infiltration (Fig. 1e, f). She was referred to cranial radiotherapy. Hypopituitarism persisted in this patient.

**Patient 2**

A 67-year-old female whose case was previously reported by Pekic and colleagues [10]. She had a 3-month history of nonspecific symptoms (malaise, fatigue, night sweats, nausea, vomiting, fever and weight loss). On clinical examination she was pale, with dry skin, with no lymphadenopathy or hepatosplenomegaly. Laboratory analysis showed elevated ESR, anemia, thrombocytopenia, normal leukocyte count and elevated serum LDH (Table 1). Bone marrow analysis showed intravascular B cell lymphoma (Fig. 3a–c). She also had hyponatremia (128 nmol/L) at presentation, which triggered further endocrine assessment. Hormonal evaluation at baseline revealed low gonadotropin levels, low total thyroxine and low normal free thyroxine levels with low TSH levels, low normal cortisol concentrations and low IGF-1 level in comparison with a sex- and age-matched healthy subject. We performed a stimulation test for growth hormone (GH) secretion, the combined GHRH + GHRP-6 test. A low GH peak (3.93 μg/L, normal >20 μg/L), indicated severe GH deficiency. The prolactin level was normal and she had no central diabetes insipidus (Table 1). She was replaced with prednisolone (5 mg/d) and levothyroxine (50 μg/d). Her MRI scan performed at baseline, before starting prednisolone, showed partial empty sella (Fig. 4a, b). She was treated with immunochemotherapy (six cycles

---

**Fig. 1** Non Hodgkin B follicular lymphoma (Patient 1)

a) X-radiography of the scull showing enlarged, destructed sella. b–d) Sellar magnetic resonance image (MRI) at baseline (b—coronal section, c—sagittal section, d—axial section) showing the presence of symmetric sellar and suprasellar mass with invasion of both cavernous sinuses. e–f) Sellar MRI, 6 months after the beginning of the chemotherapy (e—coronal section, f—sagittal section) showing the significant regression of the pathological involvement of the sellar region.
Table 1  Laboratory and hormonal parameters in patients with hematological malignancies in sellar region

| Parameter               | Pt 1.   | Pt 2.   | Pt 3.   | Pt 4.   | Pt 5.   | Reference range    |
|-------------------------|---------|---------|---------|---------|---------|-------------------|
| Age (years)             | 53      | 67      | 53      | 46      | 57      |                   |
| Gender                  | female  | female  | female  | female  | female  |                   |
| ESR (mm/h)              | 74      | 76      | 110     | 48      | 100     |                   |
| Hemoglobin (g/L)        | 100     | 64      | 100     | 95…60  | 118     | 0–30              |
| Erythrocytes (×10^{12}/L)| 2.99    | —       | 3.1     | 2.9…1.9| 3.75    | 3.86–5.08         |
| Leukocytes (×10^{9}/L)  | 6.4     | 4.3     | 18.7    | 6.7…37.1| 6.65    | 3.4–9.7           |
| Platelets (×10^{3}/L)   | 100     | —       | 36      | 640…666| 244     | 158–424           |
| LDH (U/L)               | 681     | 1,751   | 3,316   | 947…2,379| 322    | 220–460           |
| Ca (mmol/L)             | 2.35    | —       | 2.9     | 2.41    | 3.5     | 2.15–2.65         |
| FT4 (pmol/L)            | 5.9     | 7.1     | 16.9    | —       | 12.6    | 7–18              |
| T4 (nmol/L)             | —       | 34.7    | —       | 147     | —       | 55–160            |
| TSH (mIU/L)             | 2.0     | 0.4     | 1.8     | 0.68    | 1.8     | 0.15–5.0          |
| Cortisol (nmol/L)       | 193     | 213     | 741     | 425     | 590     | 131–642           |
| ACTH (ng/L)             | 7.0     | —       | 14.4    | —       | —       |                   |
| FSH (IU/L)              | 2.1     | 1.1     | 5.8     | 37.6    | 98.0    | 19–130            |
| LH (IU/L)               | 5.2     | 0.85    | 2.5     | 27.9    | 16.7    | 12–58             |
| Prolactin (mIU/L)       | 1,165   | 478     | 406     | 389     | 631     | 44–530            |
| IGF-I (ng/mL)           | 34      | 45      | 53.2    | 68.2    | 300     |                   |
| (reference range)       | (87–238)| (69–200)*| (87–238)| (94–252)**| (81–225)*****|                   |
| PTH (ng/L)              | —       | 7.0     | —       | —       | 15      | 15–65             |

ERS—erythrocyte sedimentation rate

* Pt 2. GHRH + GHRP-6 peak GH 3.93 μg/L (normal >20)
** Pt 4. ITT peak GH 29.3 mIU/L; peak cortisol 698 nmol/L, peak PRL 2,420 mIU/L
*** Pt 5. Oral glucose tolerance test (OGTT): at baseline - growth hormone (GH) 0.2…0.6…4.3…2.4…1.8 μg/L; after 3 cycles of chemotherapy–GH 0.3 (0 min)… 0.2 μg/L (120 min)

Fig. 2  Non Hodgkin B follicular lymphoma (Patient 1)

a) Lymphoid tumor tissue was composed of small cells (HE, magnification 400×). B-cell neoplasm was proven by diffuse CD20 (b) and PAX5 (c) positivity (magnification 400×). Tumor cells were positive for bcl-2 (d). Germinal center markers bcl-6 (e) and CD10 (f) were also positive (magnification 400×).
of rituximab-CHOP), resulting in hematologic remission and partial recovery of anterior pituitary function [10]. Serum IGF-1 and gonadotropin levels increased gradually during immunochemotherapy. Between chemotherapy cycles, she was replaced with 5 mg/d of prednisolone, which was discontinued after three months of chemotherapy. An initial attempt to withdraw levothyroxine during immunochemotherapy failed. After normalization of bone marrow findings indicating hematologic remission, an ITT was performed showing low GH peak (1.94 μg/L) and normal cortisol response (peak cortisol response above 500 nmol/L), indicating the persistence of severe GH deficiency and recovery of the corticotropin axis. The stimulatory GHRH + GHRP-6 test was repeated 18 and 24 months after complete hematologic remission showing gradual improvement (peak GH level 13.3 μg/L at 18 months) and finally normalization of the somatotroph axis (peak GH levels 20.1 μg/L at 24 months). Thyroid status also returned to normal when levothyroxine replacement was discontinued. In conclusion, during the long follow-up (24 months after complete hematologic remission) the patient showed gradual complete reversal of hypopituitarism [10].

Patient 3
A 53-year-old female presented with acute onset diplopia, left eye ptosis and malaise for 15 days. She had regular menstrual cycles. She was pale, dehydrated, with left-sided CN III and right-sided CN VI palsies. She had hypercalcemia, elevated ESR, anemia, leukocytosis, thrombocytopenia and elevated serum LDH (Table 1). An MRI scan revealed an expansive process in the sellar region, with bilateral cavernous sinus infiltration (Fig. 5a, b). Over the following two days she developed rapid progression of leukocytosis (18,7…28,8…36,6 × 10⁹/L), with decrease of hemoglobin (100…92…87 g/L) and platelets number (36…25…25 × 10⁹/L). Her parathyroid hormone level was suppressed (Table 1). Baseline hormonal status was normal, except for low IGF-I level (Table 1). Bone marrow analysis showed high grade non-Hodgkin B lymphoma in leukemic phase, with proliferative Ki-67 index 90%. She was treated with dexamethasone (12 mg/d) for 12 days and her condition improved, with normalization of diplopia and calcium level, and resolution of the sellar lesion (Fig. 5c, d). She was started on immunochemotherapy protocol (R-HYPER CVAD), but she died after the first cycle.

Patient 4
A 46-year-old female presented with polyuria and polydipsia (7–10 L/day) during 14 days, after acute respiratory infection. Her menstrual cycles had become irregular a few months prior. She had elevated ESR, anemia, leukocytosis, thrombocytosis and elevated LDH (Table 1). At presentation she was afebrile, pale, with no lymphadenopathy or hepatosplenomegaly. Central diabetes insipidus was diagnosed on the basis of elevated serum osmolality (300 mOsmol/L), low urine osmolality (47 mOsmol/L) and sellar MRI scan revealing absence of the physiological hyperintensity of neurohypophysis (“bright spot”) in T1-weighted images. She was replaced...
with desmopressin (DDAVP). A month later she was subfebrile, with rapid increase of leukocyte numbers (6.7…16.3…37.1 × 10^9/L), decrease of erythrocyte count (2.9…2.2…1.9 × 10^{12}/L) and increase in LDH (947…1,338…2,379 IU/L). Bone marrow examination revealed acute myeloid leukemia. She started chemotherapy, but died after 4 months.

**Patient 5**

A 57-year-old-female presented with acute onset of headache, left eye ptosis, diplopia and dizziness, which lasted for 30 days. On physical examination she had left-sided CN III and right-sided CN VI palsies, persistently present but oscillating in severity. She had elevated ESR, anemia and hypercalcemia (Table 1). On cranial X-radiography multiple, small, lytic, punched-out round skull lesions and a destructed sella were described (Fig. 6a). A sellar MRI scan showed intra, supra and infrasellar expansive lesion with bilateral cavernous sinus sphenoid sinus and clivus infiltration (Fig. 6b–d). Baseline hormonal evaluation showed normal anterior pituitary function, with slightly elevated prolactin level and IGF-I (Table 1). A paradoxical growth hormone increase upon oral glucose tolerance test was observed (Table 1). No clinical signs of acromegaly were present. Other possible explanations for elevated IGF-1, beside acromegaly, such as renal insufficiency or oral contraceptive use, were excluded in our patient. Parathyroid hormone level was suppressed, which was in line with malignancy-related hypercalcemia (Table 1). Serum immuno-electrophoresis showed monoclonal IgA of kappa type. Serum calcium was normalized by intravenous zolendronate 4mg. Bone biopsy revealed multiple myeloma of kappa type (80% of plasmacytes, CD38+, CD138+, kappa+). She

---

**Fig. 5** Leukemic phase of Non Hodgkin B lymphoma (Patient 3)

a–b) Sellar MRI at baseline (a—coronal section, b—sagittal section) showing symmetric infiltration of the pituitary, with invasion of both cavernous sinuses. c–d) Sellar MRI after 12 days of dexamethasone therapy (c—coronal section, d—sagittal section) showing significant reduction of pituitary infiltration.

**Fig. 6** Multiple myeloma (Patient 5)

a) X-radiography of the skull showing multiple, small, lytic, punched-out round lesions within the skull and destructed sella. b–d) Sellar magnetic resonance image (MRI) at baseline (b—coronal section, c—sagittal section, d—axial section) showing the presence of intra, supra and infrasellar expansive lesion with infiltration of both cavernous sinuses, sphenoid sinus and clivus. e–f) Sellar MRI, 3 months after the beginning of the chemotherapy (e—coronal section, f—sagittal section) showing the significant regression of the pathological involvement of the sellar region.
was referred to transsphenoidal decompression. Tumor tissue was analyzed with hematoxylin-eosin for the morphological evaluation and the hematological diagnosis of multiple myeloma IgA kappa+ was confirmed with immunohistochemistry (plasma cells were positive for CD38 and CD138, while monoclonal proliferation was proven by positivity for kappa light chain) (Fig. 7a–e). She was referred to the hematological department for treatment with thalidomide and dexamethasone. After five days of therapy she developed malignant hypercalcemia (4.7 mmol/L) and acute renal failure. She was rehydrated, treated with zolendronate, then switched to bortezomib and dexamethasone. After three cycles of chemotherapy, the IGF-1 level was unchanged (322 ng/mL), with marginally elevated IGFBP-3 (1.04 ULN), and repeated OGTT revealed normal GH suppression (Table 1). After the three cycles of therapy, her CN palsies were resolved and her MRI scan showed a reduction of intrasellar infiltration (Fig. 6e, f).

Discussion

The sellar region is the site of a wide variety of neoplastic processes (mainly pituitary tumors), but also of various vascular, inflammatory, infiltrative and infectious lesions. Hematological malignancies involving the pituitary are exceedingly rare. The present case series of 5 hematological neoplasms, primarily diagnosed due to sellar region involvement among 1,405 patients with sellar region pathology over the course of 17 years in a tertiary care center, seem relatively large compared to experience at other centers of excellence. In a large German study of 4,122 sellar masses, only one patient with lymphoma in that region was reported [11]. In a retrospective study of 2,598 patients undergoing pituitary MRI scan, two patients had pituitary B-cell lymphoma, one patient had primary CNS lymphoma with pituitary stalk infiltration, and one patient had nasopharyngeal lymphoma invading the parasellar region with no effect on the pituitary gland [12]. In a large series of 380 patients with metastasis to the pituitary, five patients had leukemia (1.3%), three patients had multiple myeloma (0.8%) and 2 patients (0.5%) had lymphoma [1]. However, in a large study of 137 patients with pituitary stalk thickening, there were 84 patients with malignant tumors, 14 of them metastases mainly from the lung and breast, but no case of lymphoma or other hematological malignancies was identified [13].

Primary pituitary lymphoma. There are case reports and a few large studies of primary pituitary lymphoma [8, 14-16]. The majority of cases were B-cell lymphomas (more than 80%), while other cases of non-Hodgkin lymphoma (Burkitt, T-cell, NK/T cell lymphoma, MALT) and Hodgkin lymphoma involving the pituitary have been reported even more rarely [8, 15-20]. Nasopharyngeal B-cell lymphoma may also infiltrate the pituitary region, causing hypopituitarism and cranial nerve palsy [21]. In systemic lymphoma, neural cell adhesion molecule (NCAM) or other molecular expression in peripheral lymphoma cells may lead to the homing and
proliferation of lymphoma cells in the CNS and pituitary gland [22]. In some cases, lymphoid B-cells are negative for intercellular adhesion molecule 1 (ICAM1) and β1 integrin (CD29), the surface molecules necessary for diapedesis across the endothelium. This is intravascular lymphoma (IVL), a rare and aggressive type of B-cell lymphoma, with massive proliferation of lymphoid cells in small and medium blood vessel lumens causing their occlusion by neoplastic cells [23]. One of our patients had IVL with empty sella and hypopituitarism. Women are predominately affected, with a mean age of 64 years at diagnosis, as in our case [23]. There are 20 cases of intravascular large B-cell lymphoma involving the pituitary gland, including one described by us [10, 18, 23]. In most cases pituitary mass was described, or the pituitary gland was normal, or with partial empty sella, with hypopituitarism, in some cases reversible after hematological remission [10, 18, 23]. Pituitary CNS lymphoma occurs mainly in immunodeficient patients (in association with acquired immunodeficiency syndrome AIDS, Epstein-Barr virus infection or following organ transplantation), or in elderly immunocompetent patients, with a median age of 65 to 70 years [3, 17]. Our patients were immunocompetent, middle aged females (mean age 55.2 years). In other studies, there was male predominance with sellar lymphoma (57%), or absence of significant gender differences [8, 15, 16].

The clinical presentation of sellar hematological malignancy is usually acute or subacute, and nonspecific. In our two patients, symptoms and signs of a pituitary mass developed rapidly over 2 weeks. These rapidly growing sellar masses with aggressive infiltration of adjacent tissues, or a sudden onset of headache, ophthalmoplegia, hypopituitarism, or diabetes insipidus, strongly suggest unusual pathologies in the sellar region, and not pituitary adenoma [1]. In the case of infiltration of neurovascular structures of the cavernous sinus, clinical signs and symptoms include ophthalmoplegia, diplopia, facial sensory loss, Horner’s syndrome, chemosis and proptosis [24]. In our patients the most common presenting symptom of pituitary hematological malignancy was cranial nerve palsy, followed by headache and visual impairments. The patients with visual field defects had better prognosis, potentially due to earlier diagnosis [8]. In some patients, expansive sellar mass may be the first sign of an otherwise unrecognized hematological malignancy. Systemic symptoms and some abnormal laboratory parameters (such as ESR, blood count, LDH levels, presence of paraprotein), more specific for hematological diseases, could support diagnosis of sellar hematological malignancy, as was the case in most of our patients [16]. All our patients were in poor general condition, with malaise, and all of them had elevated ESR and disturbed blood count. Two of them also had malignancy-related hypercalcemia, while the patients with lymphoma had elevated LDH.

Hypopituitarism is common in patients with sellar hematological malignancy, except in multiple myeloma [8]. Anterior pituitary hormone deficiencies are present in 70–100% of patients with sellar lymphoma, attributed to pituitary gland infiltration by lymphoma cells [8, 15, 16]. Lymphoma cells may also infiltrate the hypothalamus causing central diabetes insipidus [25]. In large studies, diabetes insipidus developed in 30.8%–36% of patients [15, 16]. In our study, hypopituitarism was present in two out of five patients (both with lymphoma); the patient with AML had isolated diabetes insipidus, while hyperprolactinemia due to compression of the pituitary stalk was present in three patients. Hypothalamo-pituitary dysfunction may recover (fully or partially) after treatment of lymphoma or may persist, necessitating lifelong hormone replacement therapy [10, 15, 16, 20, 21, 26, 27]. In our study, hypothalamo-pituitary dysfunction completely normalized in the patient with IVL, the only one with long lasting remission.

MRI imaging is crucial for differential diagnosis of sellar masses. The sellar lymphoma presents most frequently as a diffuse and invasive mass when examined with typically intense and usually homogeneous gadolinium contrast enhancement, with intermediate to low T2 signal intensity [24, 28]. Due to high cellularity and high nucleus-to-cytoplasm ratio they show restricted diffusion on diffusion-weighted imaging [24, 29]. Due to rapid growth of the hematological malignancy, the sella is not enlarged, but sellar bone erosions may be detected [6]. Patients in our study had similar sellar changes on MRI, without a straightforward diagnosis, presumably due to the rarity of hematological neoplasms in the sellar region. Hematological malignancies in pituitary adenoma have also been reported [16]. In some cases, the MRI showed no mass lesions in the pituitary [26]. Advanced MRI techniques (perfusion, diffusion and spectroscopy) and metabolic imaging (FDG-PET-CT scan) may be needed for more precise diagnosis [24, 26, 30]. However, differentiating pituitary hematological malignancy from pituitary adenoma or other sellar pathologies by MRI is often challenging.

The histological examination of pituitary mass is considered the gold standard for diagnosis. The tissue for pathohistological diagnosis is obtained by surgery aimed at biopsy or transsphenoidal decompression. In two out of five cases in our study the diagnosis of hematological malignancy was performed on the tissue provided by transsphenoidal surgery; subsequent bone marrow biopsy was performed for the staging of the disease. Immunohistochemistry is necessary for differential diagnosis
between different types of hematological neoplasms and for differential diagnosis from non-neoplastic lesions like hypophysitis. In rare cases, the co-existence of pituitary lymphoma with pituitary adenoma, pituitary hyperplasia or hypophysitis was reported [15, 19, 31-34]. It is important to consider pituitary lymphoma in cases of suspected lymphocytic hypophysitis, especially in cases previously treated with glucocorticoids (since this therapy could change the pathohistological image of lymphoma). Symptoms, endocrine complications and radiological presentation may be the same. The further diagnostic evaluation should be considered in such cases (CT scan of the neck, chest, abdomen and pelvis and/or FDG-PET-CT scan, and biopsy of enlarged lymph nodes).

Surgery is indicated in patients with severe headache, ophthalmoplegia and visual field loss due to suprasellar extension of the tumor with optic chiasm compression, or when pathohistological diagnosis is necessary and can be made only by a pituitary approach. In our study, two patients were operated by a transsphenoidal approach and histological diagnosis confirmed diffuse large B cell lymphoma in one and multiple myeloma in the other. The patient should be scanned by full body CT scan and/or 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) due to the likelihood of a systemic disease involvement. Treatment of pituitary lymphoma is proceeded according to the hematological protocols and consists of high-dose methotrexate, immunotherapy (rituximab) and radiation therapy. Stereotactic sellar radiosurgery is effective. The complete response can be achieved in about half of patients, with a high risk of relapse within the first months after the end of therapy [3].

**Acute and chronic leukemia** may also present as a sellar mass lesion, thickened pituitary stalk or infiltration of a pituitary adenoma by leukemic cells [34-40]. An autopsy study of more than 1,200 patients who died due to acute or chronic leukemia showed that up to 20% of patients had infiltration of the pituitary gland [41]. Among the types of leukemia, chronic lymphocytic leukemia showed the highest (20%), while acute myeloid leukemia the lowest (9%) preference for pituitary involvement [41]. In our series, one patient had AML and presented with diabetes insipidus, while another patient was in the leukemic phase of non-Hodgkin B-cell lymphoma. In the literature, there are 84 cases of AML with diabetes insipidus, associated with worse outcomes [38, 42-44]. The underlying mechanism of diabetes insipidus in these 84 patients is still unclear since some patients may present with normal sellar MRI finding. In other cases, infiltration of the hypothalamus, pituitary stalk or posterior pituitary, thrombosis of small vessels of the hypothalamic-pituitary region and pituitary infarction were described [36, 43, 44]. In some patients, loss of the normal posterior pituitary hyperintensity (“bright spot”) was reported, as in our patient, implying the leukemic infiltration of vasopressin-producing neurons or karyotypic abnormalities which could affect the synthesis, secretion and transport of vasopressin [42, 43]. In some patients with AML and diabetes insipidus the molecular genotyping showed an association of monosomy 7 and chromosome 3 rearrangements [38, 42-44]. The neutrophil migration (NM) gene located on chromosome 7 is important for production of the glycoprotein gp130, a cell surface marker on granulocytes involved in neutrophil chemotaxis, migration and possibly leukemic infiltration of the pituitary gland [43, 44]. Chromosome 3 rearrangements may affect the expression of the ectopic virus integration site 1 (EVI-1) gene which is important for neural cell function, inhibition of vasopressin synthesis or secretion and impaired vasopressin transport [45]. In general, diabetes insipidus is associated with a worse prognosis.

**Multiple myeloma** is a multifocal malignancy of plasma cells, with osteolytic lesions, bone pain, pathological fractures, hypercalcemia, anemia, and renal impairment as the most common presenting symptoms. Confirming the presence of a serum monoclonal paraprotein supports the diagnosis of multiple myeloma. Intracranial localization of the disease is rare. In a study of 273 patients with multiple myeloma, only 3% exhibited intracranial involvement [46]. In some cases, extramedullary multiple myeloma involved only the sellar region as solitary plasmacytoma mimicking pituitary adenoma or constituting part of a systemic disease [47, 48]. The patients usually presented with headache, cranial nerve neuropathies, diplopia and/or visual field disturbances [47, 48]. In our case series, we described one patient with multiple myeloma presenting as a sellar mass with cranial nerve palsy. In the majority of published cases and in our patient, the pituitary function was well preserved, despite destruction of the pituitary fossa. After initial surgical intervention, adjuvant therapy consists of radiotherapy, chemotherapy and in some cases autologous peripheral blood stem cell transplantation [48].

In our patient with multiple myeloma affecting the sellar region we measured slightly elevated IGF-1 and paradoxical rise of GH during OGTT (possibly related to hypothalamic impairment due to suprasellar extension of the tumor) [49]. Pathohistological immunohistochemical analysis of the material provided by transsphenoidal surgery excluded any traces of pituitary adenoma or GH positive staining. Repeated OGTT after three cycles of chemotherapy, upon regression of suprasellar extension of multiple myeloma, reflected normal GH suppression.

By expressing the 95th percentile of population-based
values as the upper limit of normal for serum IGF-1, 2.5% of the normal population is expected to have IGF-1 somewhat above this limit. We consider this probable in the case of our patient. In the view of clinically and histologically excluded acromegaly, her mildly elevated IGF-1 (unaffected by treatment), could not be attributed to multiple myeloma as its source, but may have played a role in disease occurrence or progression. Population-wide studies associated a high normal IGF-1 with increased risk of various malignancies, including breast, prostate, lung and colorectal cancer [50]. In previous studies, elevated IGF-1 was not confirmed in multiple myeloma (MM) patients, but higher serum IGF-1 level was associated with worse prognosis of the disease [51]. IGF-1 signaling is believed to play a significant role in homing, progression and treatment resistance in MM [52]. We thus speculate that our patient had slightly higher serum IGF-1 as an outlier of normal, while this may have played a role in MM occurrence or progression.

In conclusion, the differential diagnostic work-up of patients with non-typical pituitary mass remains a challenge. Nonpituitary hematological malignancy in the sellar region should be suspected in a patient with an invasive sellar mass, with rapid tumor growth with cranial nerve palsies and involvement of cavernous sinuses. Malignancy-related hypercalcemia in a patient with sellar mass should prompt a wide search for the cancer source and raise suspicion of a metastatic nature of the sellar mass. Pathological findings in blood cell count, ESR and LDH may be useful as a clue to suspected hematological malignancy. Systemic hematological treatment is promising, with the possibility of anterior pituitary function restoration.

Acknowledgments

Funding
This study was supported by a grant from the Ministry of Science of Republic of Serbia (Project 175033).

Disclosure
None of the authors have any potential conflicts of interest associated with this research.

References

1. Komninos J, Vlassopoulou V, Protopapa D, Korfias S, Kontogeorgos G, et al. (2004) Tumors metastatic to the pituitary gland: case report and literature review. J Clin Endocrinol Metab 89: 574–580.
2. Jonkhoff AR, Huijgens PC, Schreuder WO, Teule GJ, Heimans JJ (1993) Hypophyseal non-Hodgkin’s lymphoma presenting with clinical panhypopituitarism successfully treated with chemotherapy. J Neurooncol 17: 155–158.
3. Franceschi E, Frappaz D, Rudá R, Hau P, Preusser M, et al. (2020) Rare primary central nervous system tumors in adults: an overview. Front Oncol 10: 996.
4. Manojlović-Gacic E, Rostami E, Karavitaki N, Casar-Borota O (2020) Histopathology of parasellar neoplasms. Neuroendocrinology 110: 805–808.
5. Shimon I (2020) Metastatic spread to the pituitary. Neuroendocrinology 110: 805–808.
6. He W, Chen F, Dalm B, Kirby PA, Greenlee JD (2015) Metastatic involvement of the pituitary gland: a systematic review with pooled individual patient data analysis. Pituitary 18: 159–168.
7. Cossu G, Brouland JP, La Rosa S, Camponovo C, Viaroli E, et al. (2019) Comprehensive evaluation of rare pituitary lesions: a single tertiary care pituitary center experience and review of the literature. Endocr Pathol 30: 219–236.
8. 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.
9. Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, et al. (2017) Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Intensive Care Med 43: 1751–1763.
10. Pekic S, Milicevic S, Colovic N, Colovic M, Popovic V (2008) Intravascular large B-cell lymphoma as a cause of hypopituitarism: gradual and late reversal of hypopituitarism after long-term remission of lymphoma with immunotherapy. Endocrine 34: 11–16.
11. Saeger W, Luedecke DK, Buchfelder M, Fahrbusch R, Quabbe HJ, et al. (2007) Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. Eur J Endocrinol 156: 203–216.
12. Famini P, Maya MM, Melmed S (2011) Pituitary magnetic resonance imaging for sellar and parasellar masses: ten-year experience in 2,598 patients. J Clin Endocrinol Metab 96: 1633–1641.
13. Zhou X, Zhu H, Yao Y, Lian X, Feng F, et al. (2019) Etiological spectrum and pattern of change in pituitary stalk thickening: experience in 321 patients. J Clin Endocrinol Metab 104: 3419–3427.
14. Ogilvie CM, Payne S, Evanson J, Lister TA, Grossman AB (2005) Lymphoma metastasing to the pituitary: an unusual presentation of a treatable disease. Pituitary 8: 139–146.
15. Tarabay A, Cossu G, Berhouma M, Levivier M, Daniel RT, et al. (2016) Primary pituitary lymphoma: an update of the literature. *J Neurooncol* 130: 383–395.
16. Caputo M, Prencipe N, Bisciglia A, Bona C, Maccario M, et al. (2020) Primary pituitary lymphoma as rare cause of a pituitary mass and hypopituitarism in adulthood. *Endocr Pract* 26: 1337–1350.
17. 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.
18. Yasuda M, Akiyama N, Miyamoto S, Warabi M, Takahama Y, et al. (2010) Primary sellar lymphoma: intravascular large B-cell lymphoma diagnosed as a double cancer and improved with chemotherapy, and literature review of primary parasellar lymphoma. *Pituitary* 13: 39–47.
19. Gupta RK, Saran RK, Srivastava AK, Jagetia A, Garg L, et al. (2017) T cell lymphoblastic lymphoma/leukemia within an adenocorticotrophic hormone and thyroid stimulating hormone positive pituitary adenoma: a cytogenetically correlating emphasizing importance of intra-operative squash smear. *Neuropathology* 37: 358–364.
20. Seymour M, Robertson T, Papacostas J, Morris K, Gillespie J, et al. (2021) A woman with visual loss, amnionrheoa and polyuria: the first reported case of nodular lymphocyte-predominant Hodgkin lymphoma presenting with hypopituitarism. *Endocrinol Diabetes Metab Case Rep* 2021: 20-0100.
21. Zahedi M, Hizomi Arani R, Tohidi M, Haghighi S, Mehrpour M, et al. (2020) Nasopharyngeal B-cell lymphoma with pan-hypopituitarism and oculomotor nerve palsy: a case report and review of the literature. *BMC Endocr Disord* 20: 163.
22. Kern WF, Spier CM, Hanneman EH, Miller TP, Matzner M, et al. (1992) Neural cell adhesion molecule-positive peripheral T-cell lymphoma: a rare variant with a propensity for unusual sites of involvement. *Blood* 79: 2432–2437.
23. Naito K, Suzuki S, Ohwada C, Ishiwata K, Ruike Y, et al. (2021) ICAM1-negative intravascular large B-cell lymphoma of the pituitary gland: a case report and literature review. *AACE Clin Case Rep* 7: 249–255.
24. Munawar K, Nayak G, Fatterpek RM, Sen C, Zagzag D, et al. (2020) Cavernous sinus lesions. *Clin Imaging* 68: 71–89.
25. Antic A, Smiljanic M, Bila J, Jankovic S, Todorovic M, et al. (2012) Hypothalamic dysfunction in a patient with primary lymphoma of the central nervous system. *Neurosci Lett* 33: 387–390.
26. Kenchaiah M, Hyer SL (2011) Diffuse large B-cell non Hodgkin’s lymphoma in a 65-year-old woman presenting with hypopituitarism and recovering after chemotherapy: a case report. *J Med Case Rep* 5: 498.
27. Takao K, Tani A, Suwa T, Kuwabara-Ohmura Y, Nonomura K, et al. (2021) Diagnosis and treatment of primary central nervous system lymphoma with the primary lesion in the hypothalamus: a case report. *BMC Endocr Pract* 21: 13.
28. Bühring U, Herrlinger U, Krings T, Thiex R, Weller M, et al. (2001) MRI features of primary. Central nervous system lymphomas at presentation. *Neurology* 57: 393–396.
29. Tsang M, Cleveland J, Rubenstein JL (2020) On point in primary CNS lymphoma. *Hematol Oncol* 38: 640–647.
30. Zacharia TT, Law M, Naidich TP, Leeds NE (2008) Central nervous system lymphoma characterization by diffusion-weighted imaging and MR spectroscopy. *J Neuroimaging* 18: 411–417.
31. Morita K, Nakamura F, Kamikubo Y, Mizuno N, Miyauchi M, et al. (2012) Pituitary lymphoma developing within pituitary adenoma. *Int J Hematol* 95: 721–724.
32. Ban VS, Chaudhary BR, Allinson K, Santarius T, Kirollos RW (2017) Concomitant primary CNS lymphoma and FSH-pituitary adenoma arising within the sella. Entirely coincidental? *Neurosurgery* 80: E170–E175.
33. Ravidra VM, Raheja A, Corn H, Driscoll M, Welt C, et al. (2017) Primary pituitary diffuse large B-cell lymphoma with somatotroph hyperplasia and acromegaly: case report. *J Neurosurg* 126: 1725–1730.
34. Abushamati LA, Kerr JM, Lopes BS, Kleinschmidt-DeMarters BK (2019) Very unusual sellar/suprasellar region masses: a review. *J Neuropathol Exp Neurol* 78: 673–684.
35. Krish K, Palmer CA, Couldwell WT (2013) Combined chronic lymphocytic leukemia and prolactinoma: a rare occurrence in a patient presenting with pituitary apoplexy. *J Neurosurg* 119: 924–928.
36. Harrup R, Pham M, McInerney G (2016) Acute myeloid leukemia with diabetes insipidus and hypophysial infiltration. *Asia Pac J Clin Oncol* 12: e350–e351.
37. Pirimoglu B, Ogul H, Ozkorucu-Yildirgan D, Keskin-Yildirim Z, Kantarci M (2018) Hypophysial involvement of acute lymphoblastic leukemia. *World Neurosurg* 120: 530–531.
38. Bardin M, Ritchie D, McLachlan R, Yates CJ (2019) Acute myeloid leukaemia presenting with diabetes insipidus. *Intern Med J* 49: 785–788.
39. Faje A (2020) Chronic lymphocytic leukemia, a rare cause of pituitary stalk thickening. *Clin Case Rep* 8: 1319–1320.
40. Fridlyand DM, Keller FG, Sabnis HS, Patterson BC, Gadde JA, et al. (2020) Very late recurrence of B-cell acute lymphoblastic leukemia masquerading as a pituitary tumor. *Pediatr Hematol Oncol* 37: 438–444.
41. Barcos M, Lane W, Gomez GA, Han T, Freeman A, et al. (1987) An autopsy study of 1206 acute and chronic leukemias (1958 to 1982). *Cancer* 60: 827–837.
42. Müller CI, Engelhardt M, Laubengerger J, Kunzmann R, Engelhardt R, et al. (2002) Myelodysplastic syndrome in transformation to acute myeloid leukemia presenting with diabetes insipidus: due to pituitary infiltration association with abnormalities of chromosomes 3 and 7. *Eur J Haematol* 69: 115–119.
43. Cull EH, Watts JM, Tallman MS, Kopp P, Frattini M, et al. (2014) Acute myeloid leukemia presenting with
panhypopituitarism or diabetes insipidus: a case series with molecular genetic analysis and review of the literature. *Leuk Lymphoma* 55: 2125–2129.

44. Lê HH, Lengelé JP, Henin M, Toffoli S, Mineur P (2021) Diabetes insipidus and acute myeloid leukemia harboring monosomy 7: report of two cases and literature review. *Acta Clin Belg* 76: 132–135.

45. Lavabre-Bertrand T, Bourquard P, Chiesa J, Berthéas MF, Lefort G, *et al.* (2001) Diabetes insipidus revealing acute myelogenous leukaemia with a high platelet count, monosomy 7 and abnormalities of chromosome 3: a new entity? *Eur J Haematol* 66: 66–69.

46. Silverstein A, Doniger DE (1963) Neurologic complications of myelomatosis. *Arch Neurol* 9: 534–544.

47. Sinnott BP, Hatipoglu B, Sarne DH (2006) Intrasellar plasmacytoma presenting as a non-functional invasive pituitary macro-adenoma: case report & literature review. *Pituitary* 9: 65–72.

48. DiDomenico J, Ampie L, Choy W, Lamano JB, Oyon DE, *et al.* (2018) Sellar plasmacytomas masquerading as pituitary adenomas: a systematic review. *J Clin Neurosci* 50: 20–23.

49. Hage M, Kamenický P, Chanson P (2019) Growth hormone response to oral glucose load: from normal to pathological conditions. *Neuroendocrinology* 108: 244–255.

50. Pekic S, Stojanovic M, Popovic V (2022) Pituitary tumors and the risk of other malignancies: is the relationship coincidental or causal? *Endocrine Oncology* 2: R1–R13.

51. Standal T, Borset M, Lenhoff S, Wisloff F, Stordal B, *et al.* (2002) Serum insulin-like growth factor is not elevated in patients with multiple myeloma but is still a prognostic factor. *Blood* 100: 3925–3929.

52. Bieghs L, Brohus M, Kristensen IB, Abildgaard N, Bøgsted M, *et al.* (2016) Abnormal IGF-binding protein profile in the bone marrow of multiple myeloma patients. *PLoS One* 11: e0154256.