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REPORT

Intravascular large B-cell lymphoma as a cause of hypopituitarism: gradual and late reversal of hypopituitarism after long-term remission of lymphoma with immunochemotherapy

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Abstract Intravascular large B-cell lymphoma (IVL) is a rare generally fatal disease characterized by massive proliferation of lymphoid cells within the small and medium blood vessels. Hypopituitarism has been reported only in a few fatal cases. We describe the clinical course of hypopituitarism as a complication of IVL, successfully treated with immunochemotherapy (cyclophosphamide/doxorubicin/vincristine/prednisone—CHOP) plus Rituximab anti-CD20 humanized antibody). Before immunochemotherapy, basal hormonal analysis and dynamic test for pituitary function were performed in a 67-year-old female with IVL. Endocrinological evaluation of the pituitary function was repeated after complete hematological remission and during the 2 years of follow-up. Multiple pituitary hormone deficiencies were diagnosed before therapy for IVL. Magnetic resonance imaging (MRI) of the pituitary gland showed partially empty sella. The patient was replaced with thyroxine 50 μg/day and prednisone 5 mg/day between the cycles of chemotherapy. After complete hematological remission (6 months after initial diagnosis) reversal of cortisol and gonadotropin deficiency occured. After 18 months of hematological remission there was further improvement in growth hormone (GH) response to provocative testings (partial GH deficiency), with normalization of somatotropic and thyreotropic axis after 2 years of follow-up. This is the first case of IVL complicated with hypopituitarism, treated with immunochemotherapy which resulted in complete hematological remission and gradual and late reversal of hypopituitarism.

Keywords Intravascular lymphoma · Hypopituitarism · Immunochemotherapy

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Introduction

Intravascular large B-cell lymphoma (IVL) is a rare generally fatal disease characterized by massive proliferation of lymphoid cells within the small and medium blood vessels, with little or no adjacent parenchymal involvement [1–3]. This disorder was previously known as "malignant angioendotheliomatosis" or "angiotropic large-cell lymphoma". Circulating cells can be rarely detected on blood smear analysis. Bone marrow and lymph nodes are usually without lymphoma cells. IVL commonly affects the central nervous system, resulting in progressive dementia and multiple neurologic deficits [4, 5]. Skin is the second most common site of involvement, in the form of cutaneous plaques and nodules [4]. Various neurologic and dermatologic signs, fever of unknown origin, malaise, fatigue, and elevated lactic dehydrogenase levels are the main features of the disease [4–6]. The diagnosis of IVL has been often made on postmortem examination [7]. There are only few cases in the literature of association of IVL with endocrine dysfunction [4, 8]. Here we present for the first time the case of a 67-year-old woman with IVL and hypopituitarism successfully treated with immunochemotherapy, with gradual reversal of anterior pituitary dysfunction after long-term remission of lymphoma.

Case report

A 67-year-old woman was admitted in Institute of Hematology after a 3-month history of progressive malaise, fatigue, night sweats, nausea and vomiting, intermediate-grade fever, and loss of weight. On clinical examination dry and pale skin was found. There was no hepatomegaly, splenomegaly, or enlarged lymph nodes. The family or personal history of autoimmunity or malignancy was negative in our patient.

Laboratory results showed: hemoglobin of 6.4 g/dl; platelets, 64,000/mm^3; white cell count, 4,300/mm^3; sedimentation rate, 76 mm/H, and elevated lactate dehydrogenase level (1751 UI/l). Mild hyponatremia (128,0 mEq/l) was observed while plasma potassium was normal. Diabetes insipidus was not present in our patient. Antinuclear antibodies and anti-neutrophil cytoplasmic antibodies (ANCA) were negative. Blood smear examination was unremarkable. Thoracic and abdominal ultrasonography and computed tomography were normal. Cytology, biochemical, and microbiological analyses of cerebrospinal fluid were normal.

Hematological diagnosis (pathologic findings) and treatment

Bone marrow aspirate showed hypercellularity with 8% of small lymphocytes and 10% of large lymphoid cells with 1–3 nucleoli without granules. Megakaryocytes were normal in number, size, and ploidy. Some erythroblasts were megaloblastic. Bone marrow histological analysis revealed hypercellularity, with large lymphoid cells with irregular contours and multiple nucleoli. These cells were located within the vascular system though there were rare lymphoid cells in perivascular space located between hematopoietic cells (Fig. 1a). Immunohistochemical examination confirmed that these cells belonged to the B lymphoid cell lineage (CD 20+++, CD3−, myeloperoxidase (MPO)−; Fig. 1b).

After diagnosing IVL the patient received six cycles of systemic chemotherapy (CHOP: cyclophosphamide/doxorubicin/vincristine/prednisone) plus immunotherapy with Rituximab (anti-CD20 humanized antibody).

Method (hormonal evaluation)

Persistent hyponatremia lead us to perform endocrine assessment. The patient was in a very poor condition. At baseline, free thyroxine (FT4), total thyroxine (T4), thyroid-stimulating hormone (TSH), gonadotropin levels, cortisol, insulin-like growth factor I (IGF-I), and prolactin were measured. For growth hormone (GH)/IGF-I axis we performed the most comfortable test, the combined GH releasing hormone (GHRH) + GH releasing peptide-6 (GHRP-6) test (GHRH—GEREF, Serono, Madrid, 1 μg/kg iv at 0 min plus GHRP-6—Clinalfa, Laufelingen, Switzerland, 1 μg/kg iv at 0 min). The combined GHRH + GHRP-6 test was performed after overnight fast, at 08:00 h. Samples for GH were taken at 0, 15, 30, and 45 min after bolus GHRH + GHRP-6 injection. Severe GH deficiency (GHD) is defined by a peak GH response less of 10 μg/l during the combined GHRH + GHRP-6 test, partial GHD with peak GH between 10 and 20 μg/l, and normal response with peak GH > 20 μg/l [9].

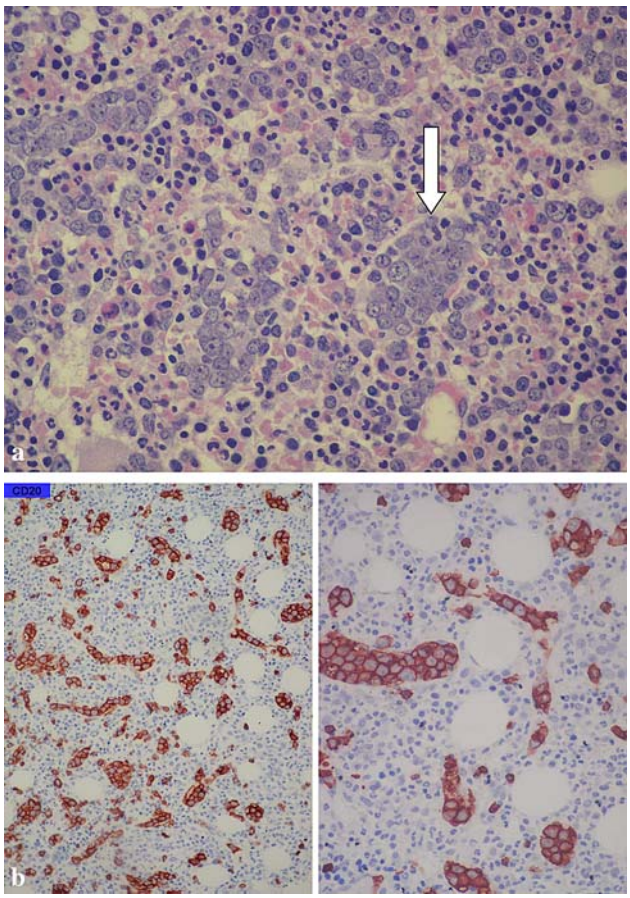

Fig. 1 **a** Hematoxilin-eosin staining of the bone marrow at the time of the diagnosis of intravascular lymphoma showing lymphoid aggregates within intrasinusoidal and small blood vessels (magnification 400×). **b** Immunohistochemistry of the bone marrow (anti-CD 20 antibodies). Intrasinusoidal B cells are immunopositive for the B cell marker CD20 (magnification: left-100×, right-200×)

Basal hormonal evaluations were repeated every month, before each cycle of immunochemotherapy, then after complete hematological remission (6 months after initial diagnosis) and during the follow-up period of 2 years (6, 18, and 24 months after complete hematological remission). Anterior pituitary reserve was tested with insulin tolerance test (ITT) after complete hematological remission (6 months after initial diagnosis), measuring GH and

cortisol at 0, 30, 60, 90, and 120 min after a bolus of 0.15 IU/kg of Actrapid-Insulin i.v. A peak GH response of less than 3 μg/l during ITT was interpreted as severe GHD, while peak cortisol response during ITT above 500 nmol/l and/or an increase from baseline of 170 nmol/l or more, was interpreted as normal hypothalamo-pituitary-adrenal (HPA) axis response [10]. After 18 and 24 months of follow-up the combined GHRH + GHRP-6 test was repeated.

Hormones were measured by commercial kits: T4 by radioimmunoassay (RIA, INEP, Zemun, Yugoslavia), FT4 by RIA (Cis BioInternational), TSH by immunoradiometric assay (IRMA, INEP, Zemun, Yugoslavia), prolactin (PRL) by IRMA (Cis BioInternational), cortisol by RIA (Cis BioInternational), luteinizing hormone (LH) by IRMA (Cis BioInternational), follicle-stimulating hormone (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).

Results

The results of hormonal evaluations are shown in Table 1.

At baseline (before immunochemotherapy) low gonadotropin levels, low total and free thyroxine levels with low TSH levels, and low/normal cortisol concentrations were registered. Prolactin level was normal. IGF-I level was low in comparison with sex- and age-matched healthy subject. Thyroid antibodies were negative. Peak growth hormone level during GHRH + GHRP-6 test was 3.93 μg/l, indicating severe growth hormone deficiency (GHD). Magnetic resonance imaging (MRI) of the pituitary gland showed partially empty sella (Fig. 2a, b). The patient received hormonal replacement therapy (thyroxine 50 μg/d and prednisone 5 mg/d).

During hematological treatment (0–6 months), hormonal evaluations showed partial recovery of anterior pituitary function. Serum gonadotropin levels (Fig. 3a) and IGF-I increased gradually during the immunochemotherapy. IGF-I level did not normalize after 6 months of therapy. The patient was replaced with prednisone (5 mg/d) between the cycles of chemotherapy for the first 3 months of therapy, and after that prednisone was discontinued. Serum cortisol levels were normal and the patient responded well to the immunochemotherapy. Upon withdrawal of thyroxine replacement, FT4 levels remained low so thyroxine was reinstituted.

Evaluation after remission of IVL (with normalization of bone marrow findings, 6 months after initial diagnosis) revealed partial recovery of pituitary function, namely the corticotropin axis. The patient was in good condition and insulin tolerance test (ITT) was performed. Cortisol levels during insulin tolerance test were normal (Fig. 3b). IGF-I serum level was low and peak growth hormone concentration during ITT was 1.94 μg/l, indicating persistence of severe GHD.

We reevaluated the endocrine status 6, 18, and 24 months after complete hematological remission. Prolactin and cortisol levels remained normal, while gonadotropin levels increased (Table 1, Fig. 3a). Hypothyroidism persisted and the patient continued thyroxine replacement therapy. IGF-I serum level was low normal. The combined GHRH + GHRP-6 test repeated 18 months after complete hematological remission showed peak GH level during this test of 13.3 μg/l, indicating improvement

Table 1 Hormonal analysis at baseline, during immunochemotherapy (0–6 months) and during the remission period (6, 18, 24, and 25 months)

Parameter (normal range)	At baseline	Immunochemotherapy						Hematological remission			
		1 month	2 months	3 months	4 months	5 months	6 months	6 months	18 months	24 months	25 months
FT4 (7–18 pmol/l)	7.1	14.7[a]	–	20.6[a]	8.4[c]	10.3[a]	7.3[a]	–	10.8[a]	14.8[a]	12.1[c]
T4 (55–160 nmol/l)	34.7	107.8[a]	114.8[a]	137.2[a]	75.2[c]	82.5[a]	107.2[a]	105[a]	137	120	–
TSH (0.2–5.9 mU/l)	0.4	0.15	0.15	0.15	1.92[c]	0.2	1.0	0.41	0.40	1.27	–
Prolactin (85–490 mU/l)	478	220	295	311	542	439	367	351	238	171.3	–
Cortisol (8 h, 131–642 nmol/l)	213.5	–[b]	–[b]	283[b]	228[c]	196	235	351	371	516	–
LH (12–58 mU/l)	0.85	0.42	3.7	4.5	6.8	4.3	9.5	9.1	7.4	7.4	–
FSH (19–130 mU/l)	1.1	11.9	16.0	16.6	18.6	16.9	24.0	26.3	37.8	25.1	–
IGF–1 (69–200 ng/ml)	45	–	–	–	98.9	69.9	–	69.6	62	–	–
Peak GH (GHRH + GHRP–6) (normal > 20 μg/l)	3.93								13.3	20.1	
Peak GH (ITT) (normal > 3 μg/l)							1.94				

[a] Thyroxine replacement therapy (50–75 μg/d), [b] Prednisone replacement therapy (5 mg/d), [c] Without thyroxine and/or prednisone replacement therapy

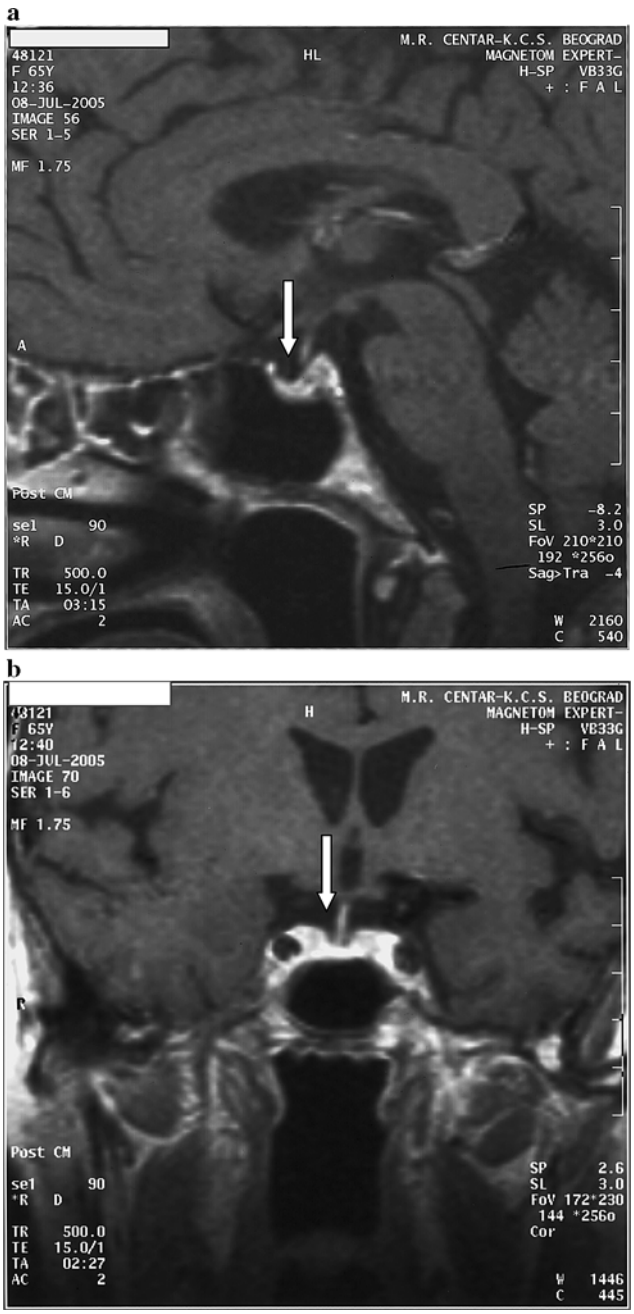

Fig. 2 Magnetic resonance imaging (MRI) of the pituitary gland (**a** sagittal image, **b** coronal image) in patient with IVL at baseline showing partially empty sella

in growth hormone secretion, i.e. partial GHD. Repeated MRI of the pituitary gland 1 year after hematological remission showed persistence of partially empty sella.

We reevaluated the somatotropic axis with GHRH + GHRP-6 test 24 months after complete hematological remission, with normalization of GH response during provocative test (20.1 μg/l; Table 1). Upon withdrawal of thyroxine replacement (during 1 month), FT4 levels was still normal (12.1 pmol/l).

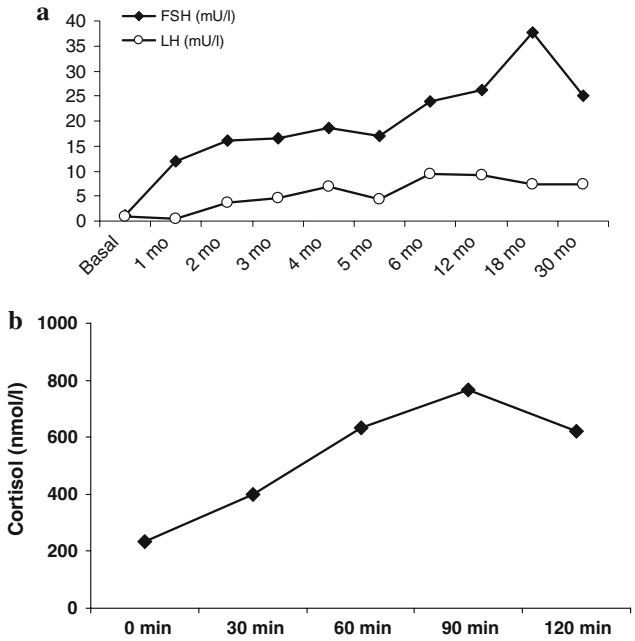

Fig. 3 **a** Gonadotropins in patient with IVL before, during the immunochemotherapy, and during the follow-up (FSH normal menopausal range, 19–130 mU/l and LH normal menopausal range, 12–58 mU/l). **b** Cortisol response to the insulin tolerance test (ITT) after six cycles of immunochemotherapy and complete hematological remission

Discussion

This is a first report of a 67-year-old woman in whom ultimately diagnosis of IVL and hypopituitarism as a clinical manifestation of IVL were established and who after successful immunochemotherapy reversed hematological abnormalities and gradually improved all endocrine dysfunctions during long-term follow-up.

IVL is an rare lymphoma often presenting with nonspecific clinical signs and symptoms and high mortality rate [4, 11]. It represents a subtype of diffuse large B-cell lymphoma which involve blood vessels with unusual predilection for the central nervous system (CNS) [5]. The classic presentation occurs in a middle-aged or older patient with dermatologic or neurologic symptoms [4, 6]. Diagnosis is often difficult because the disease is not comprised to usual lymphoid tissues sites and in 53% of patients the diagnosis is made postmortem [7, 11]. In the literature till 1999, the majority of examined bone marrow in patients with IVL were negative for tumor cells. In a case of bone marrow localization the diagnosis of IVL can be confirmed with immunohistochemical studies which show that neoplastic cells are positive on the leukocyte common antigen (CD45) and B cell markers (CD20 and CD19) [12]. In our patient anemia and thrombocytopenia were present in peripheral blood and bone marrow

immunohistochemical analysis established the correct diagnosis of IVL. At initial presentation, low serum sodium level, together with clinical symptoms and signs of hypothyroidism and hypocorticism, lead us to perform endocrinological evaluation. Basal hormonal evaluation revealed multiple pituitary hormone deficiencies (low FT4 and TSH levels, low gonadotropin and IGF-I levels, low normal cortisol level), while dynamic test for somatotropic axis revealed severe GHD. There were two possible explanations for these findings in our patient. She either had hypopituitarism as a consequence of IVL or endocrine dysfunction as a consequence of critical illness.

IVL associated with endocrine dysfunction has been described in less than 30 patients [3, 4, 8, 13]. Few reports have been focused on pituitary gland involvement in IVL with consecutive hypopituitarism [8, 13]. Krauss et al. reported four patients with IVL associated with endocrine dysfunction. Two of them had hypopituitarism, both with normal MRI scan of the pituitary gland. Both patients had normal bone marrow findings and died before IVL diagnosis. On autopsy, in both patients pituitary gland was macroscopically normal, while tumor cells were found in the pituitary microscopically. These authors reviewed the literature till 1999 and identified only 18 cases of IVL associated with endocrine disorders. In these 18 cases, hypopituitarism was demonstrated in only four patients, adrenal insufficiency in three, and hypothyroidism in one patient. Schleinitz et al. [8] described two cases of IVL associated with hypopituitarism. One patient had normal MRI scan of the pituitary gland and IVL was diagnosed by skin biopsy. She died soon after chemotherapy and complete hematological remission, without histological proof of IVL recurrence. The second patient had enlarged pituitary gland on MRI scan and IVL was diagnosed by bone marrow histological analysis. The patient died from septicemia before initiation of chemotherapy. These data demonstrated that hypopituitarism is a rare, but possible complication of IVL possibly due to infiltration of tumor cells into the vasculature of the pituitary gland producing vascular occlusions and damage of the portal blood supply. Pituitary is a highly vascularized gland. IVL frequently occludes the microvasculature of CNS and/or adrenal glands (both of neural crest origin). The mechanism for the selective intravascular growth of this neoplasm and frequent involvement of CNS and adrenal glands remain unexplained. Tissue-specific vascular homing receptors may play a role (CD 29 and CD 54). The lack of CD 29 and CD 54 adhesion molecules is reported in patients with IVL, which may contribute to intravascular and disseminated distribution pattern of IVL [14]. Consequently, chronic ischemia, and/or hemorrhage and/or infarction may occur. Necrosis of the pituitary cells occurs in next stage of the disease. In most of the cases of pituitary IVL proven by histology or autopsy, the pituitaries were enlarged, whereas normal-sized or atrophied pituitaries and empty sella have also been observed [8]. The latter patients are thought to suffer from a later stage of the disease. Spontaneous remission can occur if the pituitary tissue is not extensively destroyed. Our patient with hypopituitarism on repeated MRI, 1 year after hematological remission, still had partially empty sella. Others found normal MRI of the pituitary (which does not exclude IVL infiltration) or enlarged pituitary gland [4, 8, 13]. Gradual and late complete recovery of pituitary function (2 years after complete hematologic remission) favors the hypothesis that immunochemotherapy cured the vascular infiltration of the lymphoma cells in the pituitary gland. The possible mechanisms of the recovery of the pituitary function over time are revascularization and repopulation, which clearly requires time. The studies of Daniel et al. and Ceballos [15, 16] documented "mitotic figures among the surviving cells" and "repopulated appearance of the anterior lobe" in patients with hypopituitarism caused by traumatic brain injury (TBI). The peripheral layer of anterior pituitary cells under the capsule receives arterial blood from the capsule, not from the two systems of portal veins. These cells and those in a small area near to the posterior lobe are the only surviving cells in cases of pure anterior lobe necrosis [15]. The damaged pituitary portal vessels can regenerate and grow down into the surviving parts of the anterior lobe and permit some tissue regeneration and restoration of the anterior pituitary function. Also, in some cases of lymphocytic hypophysitis (an autoimmune disorder of the pituitary gland with pituicyte destruction by T cell-mediated cytotoxicity) and hypopituitarism [17] spontaneous partial or full recovery of pituitary function is well documented.

The second possibility for these endocrine findings might have been the critical illness of the patient which we consider unlikely for the following reasons. Although during prolonged critical illness, suppression of the neuroendocrine axes contributes to the low serum levels of the respective target organ hormones [18, 19]; upon complete hematological remission pituitary dysfunction did not resolve in our patient. Mechanisms of alterations within the hypothalamic pituitary axes during the chronic phase of critical illness remain incompletely understood [19]. Relative hyposomatotropism in prolonged critical illness is characterized with decreased pulsatile GH secretion and low circulating levels of IGF-I and IGFBP-3, but the whole somatotropic axis has been found to be very sensitive to GH releasing peptide (GHRP), with a striking GH response to GHRP-2 administered alone or in combination with GH releasing hormone (GHRH) [20, 21]. This was not the case in our patient, who had low IGF-I levels and very low GH response to the combined GHRH + GHRP-6 test at the

time of IVL diagnosis. After completing hematological therapy, the patient was well and in the hematological remission, while GH response to insulin-induced hypoglycemia remained inadequately low and recovered only after 2 years of hematological remission. Further evidence against prolonged critical illness is the slow recovery of thyreotropic axis. Low FT4 level before immunochemotherapy also normalized after more than 2 years of follow-up. In addition low-normal serum cortisol level before immunochemotherapy is in contrast with the reported increased cortisol levels during critical illness [22, 23]. Initially, due to poor condition of our patient treatment with corticosteroids was introduced, so we did not perform a cortisol stimulation test.

In conclusion, we present a female patient with anemia, thrombocytopenia, elevated serum lactate dehydrogenase level with bone marrow immunohistochemical confirmation of the diagnosis of IVL. To our knowledge, this is the first case of intravascular large B-cell lymphoma associated with hypopituitarism, successfully treated with immunochemotherapy, which resulted in complete hematological remission with gradual and late complete reversal of hypopituitarism during long-term follow-up. Further experimental and clinical studies are needed to better delineate the pathophysiology of neuroendocrine dysfunction and recovery of the pituitary function in patients with hypothalamo-pituitary pathology, including lymphoma.

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