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### EXPERT RECOMMENDATIONS

- 510** GOECP/SEOR clinical recommendations for lung cancer radiotherapy during the COVID-19 pandemic  
*Couñago F, Navarro-Martin A, Luna J, Rodríguez de Dios N, Rodríguez A, Casas F, García R, Gómez-Caamaño A, Contreras J, Serrano J*

### REVIEW

- 528** B-cell lymphoma-2 inhibition and resistance in acute myeloid leukemia  
*Wilde L, Ramanathan S, Kasner M*
- 541** Combination drug regimens for metastatic clear cell renal cell carcinoma  
*Khetani VV, Portal DE, Shah MR, Mayer T, Singer EA*
- 563** Circular RNA and its potential as prostate cancer biomarkers  
*Tucker D, Zheng W, Zhang DH, Dong X*
- 573** Statins in risk-reduction and treatment of cancer  
*Barbalata CI, Tefas LR, Achim M, Tomuta I, Porfire AS*
- 589** Novel molecular targets in hepatocellular carcinoma  
*Chow AKM, Yau SWL, Ng L*

### ORIGINAL ARTICLE

#### Retrospective Study

- 606** Effectiveness of a novel, fixed dose combination of netupitant and palonosetron in prevention of chemotherapy induced nausea and vomiting: A real-life study from India  
*Vaswani B, Bhagat S, Patil S, Barkate H*

#### Observational Study

- 614** Mutational analysis of *Ras* hotspots in patients with urothelial carcinoma of the bladder  
*Tripathi K, Goel A, Singhai A, Garg M*

### SYSTEMATIC REVIEWS

- 629** Management of neuroblastoma in limited-resource settings  
*van Heerden J, Kruger M*

### CASE REPORT

- 644** Concurrent renal cell carcinoma and hematologic malignancies: Nine case reports  
*Shields LB, Kalebastiy AR*

- 655** Proton beam therapy of periorbital sinonasal squamous cell carcinoma: Two case reports and review of literature  
*Lin YL*
- 673** Intravascular lymphoma with hypopituitarism: A case report  
*Kawahigashi T, Teshima S, Tanaka E*

## ABOUT COVER

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# Intravascular lymphoma with hypopituitarism: A case report

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## Abstract

### BACKGROUND

Intravascular lymphoma (IVL) is a rare subtype of lymphoma involving the growth of lymphoma cells within the vessel lumina without lymphadenopathy. Because of various modes of presentation and its rarity, IVL is often diagnosed postmortem. Herein, we report a case of intravascular B-cell lymphoma with hypopituitarism, an extremely rare complication, that was successfully treated with chemotherapy.

### CASE SUMMARY

An 80-year-old Japanese woman presented with a 7-mo history of a tingling sensation in the lower limbs. She also presented with various other symptoms such as pancytopenia, high fever daily, and unconsciousness with hypoglycemia. Although the doctor who previously treated her diagnosed hypoglycemia as being due to hypopituitarism, the cause of the other symptoms remained uncertain despite a 7-mo evaluation period. We performed bone marrow aspiration to evaluate pancytopenia and found that she had hemophagocytic lymphohistiocytosis (HLH). On the basis of a random skin biopsy for assessing the cause of HLH, she was diagnosed with intravascular B-cell lymphoma. HLH and hypopituitarism were considered secondary to IVL. All her clinical findings matched the presentations of IVL. She was immediately treated with chemotherapy and achieved complete response. She was relapse free two years after treatment.

### CONCLUSION

IVL should be included in the differential diagnosis of hypopituitarism, which although life-threatening, is treatable through prompt diagnosis and appropriate chemotherapy.

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**Core tip:** When encountering cases showing a variety of symptoms that cannot be reasonably explained, general physicians should consider intravascular lymphoma (IVL) and its useful diagnostic tool, *i.e.*, random skin biopsy. Additionally, the mechanisms underlying lymphoma-associated hypopituitarism associated with IVL have not yet been elucidated, thereby necessitating further case studies and laboratory-based research.

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## INTRODUCTION

Intravascular lymphoma (IVL) is a rare subtype of lymphoma, characterized by the selective proliferation of lymphoma cells within the lumina of small-to-medium-sized blood vessels<sup>[1]</sup>. A B-cell immunophenotype is most commonly observed, although cases with T-cell receptor rearrangements have also been reported<sup>[2]</sup>. Although various organs can be affected by lymphoma cells, hypopituitarism is an extremely rare complication, and limited cases have been reported<sup>[3]</sup>. We herein report a case of hypopituitarism due to IVL, which was successfully treated with chemotherapy.

## CASE PRESENTATION

### Chief complaints

An 80-year-old Japanese woman with no significant comorbidities noticed a bilateral tingling sensation on the anterior surface of her lower limbs.

### History of present illness

The sensation was localized below her thighs; however, she felt neither numbness nor weakness, and could walk and ride a bicycle without any problems. Her symptoms persisted for about one month, which resulted in a visit to a local outpatient clinic. Laboratory studies performed in the clinic showed pancytopenia. Although the patient was examined at another general hospital, the cause of her condition was unknown. Subsequently, she experienced a high fever (a temperature of 38°C - 39°C) daily. However, she did not have any other accompanying symptoms, such as chills, pain, and appetite loss, and her general state was relatively normal. Despite a more detailed evaluation, the patient's diagnosis was inconclusive, and she was observed as an outpatient. Five months after her first visit, she was taken to the emergency department of the hospital at which she was previously treated, because of sudden loss of consciousness. Laboratory studies showed that she had lost consciousness because of hypoglycemia, and further evaluation revealed that hypoglycemia was one of the signs of hypopituitarism. She received glucocorticoid and replacement therapy. Whereas treatment resulted in blood glucose level control, the tingling sensation gradually progressed. Although seven months had elapsed since her first visit, the causes of her symptoms remained unknown. Therefore, she was admitted to the Department of Hematology of our hospital for further assessment.

### History of past illness

Her past medical history was noncontributory.

### Personal and family history

Her family history was noncontributory.



### Physical examination upon admission

On physical examination, we observed the presence of a tingling sensation on the anterior regions of the lower limbs, under the thighs, and on both palms of the patient. Decreased vibratory sensation on both sides of the lower extremities was also noticed. Hepatosplenomegaly, lymph node enlargement, and skin eruption were not observed.

### Laboratory examinations

Blood test results were as follows: White blood cell count, 300 cells/ $\mu$ L; Hemoglobin level, 9.0 g/dL; and Platelet count, 113000 platelets/ $\mu$ L, lactate dehydrogenase, 971 IU/L; Ferritin, 710 ng/mL; Soluble interleukin-2 receptor alpha, 3412 U/mL. No evidence of infection or solid tumor was observed on serum examination, culture, and imaging. Brain magnetic resonance imaging (MRI), however, showed enlargement of the pituitary gland (Figure 1A and B). It did not appear to be a tumor as the entire pituitary gland was almost equally contrasted; no other abnormalities were present. We performed stimulating hormone tests, as the patient had been diagnosed with hypopituitarism in the previous hospital. The patient received an injection of four kinds of hormones [growth hormone (GH)-releasing hormone, corticotropin-releasing hormone, luteinizing hormone (LH)-releasing hormone, and thyrotropin-releasing hormone], and we monitored the levels of seven kinds of hormones [GH, LH, follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), cortisol, adrenocorticotropic hormone (ACTH), and prolactin] produced in response. Low levels of six of the seven hormones were observed, with the exception of prolactin, which confirmed the diagnosis of hypopituitarism.

### Imaging examinations

Contrast-enhanced computed tomography scans of the abdomen and pelvis showed a hepatic cyst and mild splenomegaly. There was no evidence of tumor and lymphadenopathy could not be seen. Bone marrow aspiration and biopsy, performed to evaluate pancytopenia, revealed the presence of hemophagocytic lymphohistiocytosis (HLH) (Figure 2A and B). There was no evidence of tumor involvement. She met five of eight criteria of HLH (fever  $\geq 38.5^{\circ}\text{C}$ , splenomegaly, peripheral blood cytopenia, hemophagocytosis in bone marrow, ferritin  $> 500$  ng/mL, elevated soluble IL-2 receptor alpha two standard deviations above age-adjusted laboratory-specific norms)<sup>[4]</sup>. We suspected lymphoma as a cause of HLH, as no evidence of infection or solid tumors were present. One of the most common causes of adult HLH is lymphoma. However, as the patient did not show lymphadenopathy, a random skin biopsy was performed, which showed that the tumor cells had proliferated predominantly within the small vessels of the dermis with no infiltration outside the vessels (Figure 3). Immunohistochemical staining revealed positivity for the B-cell markers CD20 and CD79a in the absence of staining for T-cell markers. These characteristics were consistent with those of intravascular large B-cell lymphoma.

## FINAL DIAGNOSIS

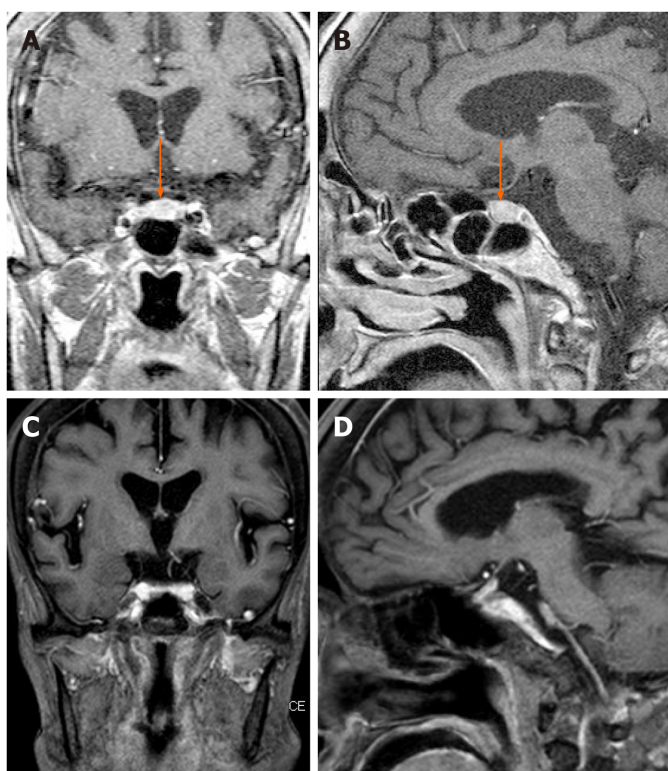
The patient was diagnosed with IVL, as well as HLH and hypopituitarism secondary to IVL.

## TREATMENT

The patient was immediately treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone. After the first chemotherapy cycle, the tingling sensation partially improved and the symptoms in the palms disappeared. Bone marrow aspiration performed after the first chemotherapy cycle demonstrated the absence of hemophagocytosis, and the bone marrow image was normal, suggesting that HLH had improved with chemotherapy. She completed six cycles of chemotherapy. After the third cycle, head MRI showed that the pituitary gland had returned to its normal size (Figure 1C and D), and it remained at that size after the six cycles. Although the patient required hormone replacement therapy after chemotherapy, her LH, FSH, TSH, free T4, ACTH, and cortisol levels, which were all lower than normal, and prolactin levels, which were higher than normal, returned to normal levels and remained so after completion of the final chemotherapy cycle (Table 1). She did not develop any signs and symptoms associated with

**Table 1** Hormonal levels before and during/after chemotherapy

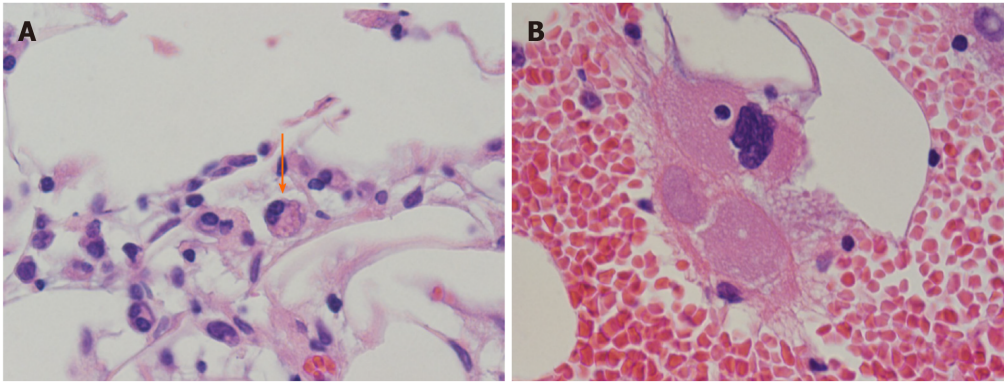
Hormone	Normal range	Before chemotherapy	During/after chemotherapy		
			After the first cycle of chemotherapy	After six cycles of chemotherapy	After 1 yr of chemotherapy
Thyroid-stimulating hormone	0.38-4.31 $\mu$ IU/mL	0.04	0.28	0.52	0.50
Free T3	2.17-3.34 pg/mL	0.71	1.17	2.39	2.00
Free T4	0.82-1.63 ng/dL	0.63	1.22	1.22	1.74
Growth hormone	0.13-9.88 ng/mL	0.68	0.33	0.35	0.24
Prolactin	3.1-15.4 ng/mL	24.20	25.60	16.80	
Adrenocorticotrophic hormone	7.2-63.3 pg/mL	5.00	10.70	1.90	< 1.5
Luteinizing hormone	5.72-64.31 mIU/mL	< 0.1	< 0.1	7.70	8.90
Follicle-stimulating hormone	0-157.79 mIU/mL	0.50	0.70	19.60	25.10
Cortisol 8 a.m.	4.5-21.1 $\mu$ g/dL	3.40	5.60	38.70	20.10



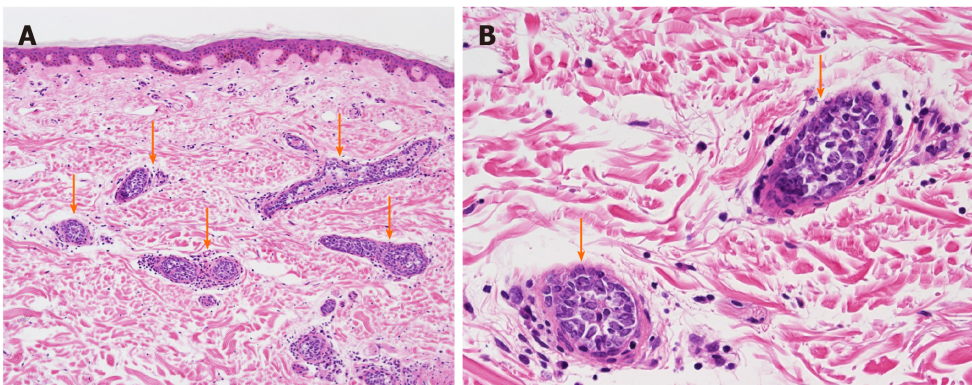
**Figure 1** Magnetic resonance imaging: T1-weighted imaging. A and B: At presentation: coronary (A) and sagittal (B) view magnetic resonance images (MRI) showing an enlarged pituitary gland; C and D: Three months later (after the third cycle of chemotherapy): Coronal (C) and sagittal (D) view MRI showing substantial mass reduction.

hypopituitarism, such as hypoglycemia, after the second cycle of chemotherapy, and her peripheral blood cell count remained normal.





**Figure 2 Bone marrow aspiration showing hemophagocytosis (designated by an arrow).** A and B: Wright and Giemsa staining at  $\times 400$  (A) and  $\times 1000$  (B) magnification.



**Figure 3 Hematoxylin and eosin.** A and B: Histopathology of intravascular lymphoma by random skin biopsy: the arrows indicate lymphoma cells seen within the lumen of small vessels: hematoxylin and eosin stain at  $\times 400$  (A) and  $\times 1000$  (B) magnification.

## OUTCOME AND FOLLOW-UP

A complete response was achieved, and the patient was relapse free two years after treatment. Although she still required minimal hormone replacement therapy, 5 mg/d of hydrocortisone, she does not show any signs of hormone deficiency.

## DISCUSSION

Antemortem diagnosis of IVL is often challenging because it affects various organs, resulting in highly variable and unpredictable presentations, although the lymph nodes are typically spared<sup>[1]</sup>. For example, the presence of a tingling sensation, which was the first complaint in this case, is a common symptom of IVL. The proliferation of tumor cells leads to multiple ischemic necrosis of the central nervous system, nerve roots, cranial nerves, and peripheral nerves<sup>[5,6]</sup>. This case highlights the importance of a random skin biopsy in diagnosing IVL. IVL is diagnosed by the identification of large lymphoma cells within small-to-medium blood vessels<sup>[7]</sup>. IVL has been reported following biopsies of various organs, such as the bone marrow, liver, and/or spleen<sup>[7]</sup>. However, with a random skin biopsy, sufficient specimens can be obtained easily with minimal invasion, and like the bone marrow trephine biopsy, it is highly sensitive for IVL diagnosis<sup>[7,8]</sup>. Sitthinamsuwan *et al*<sup>[8]</sup> demonstrate that random skin biopsy is reliable method for diagnosis of IVL especially in patients with unusual neurological symptoms with co-existing hematologic abnormalities and without lymphadenopathy, such as our case.

In this case, we observed hypopituitarism, a rare complication of IVL. Endocrinopathy is a rare presentation of IVL. Hypopituitarism associated with IVL B-cell lymphoma has been described in fewer than 20 reports<sup>[3]</sup>. The pituitary gland is a hypervascular organ, and hypopituitarism may be caused by vascular occlusion by the

lymphoid tumor cells in the hypothalamus or pituitary gland<sup>[3,9]</sup>. It is unclear why selective growth of tumor cells occurs<sup>[3,9]</sup>. Although we did not perform a pituitary biopsy, we diagnosed lymphoma infiltration of the pituitary gland based on poor evidence of other causes of hypopituitarism and pituitary gland enlargement; both conditions improved after chemotherapy. Although most patients of IVL with central nerves system involvement need intrathecal chemotherapy, most patients with pituitary involvement have responded to chemotherapy alone, as this case showed<sup>[10]</sup>.

Although the common clinical or hormonal course after treatment for pituitary involvement with IVL remains uncertain because of the limited number of reported cases, early chemotherapy may be effective. Sawada *et al*<sup>[3]</sup> described the case of a patient with hypopituitarism associated with IVL and the endocrinological course that followed. In this case, although the patient showed symptoms of panhypopituitarism before treatment, the levels of LH, FSH, TSH, ACTH, and prolactin returned to normal. She did not receive hormonal supplementation before and after chemotherapy. Sawada *et al*<sup>[3]</sup> stated that hematological therapy at an earlier disease stage may contribute to better endocrinological prognoses, and that the amelioration of pituitary infarction by chemotherapy improves pituitary function when the damage is not irreversible, enabling avoidance of hormone replacement therapy. Our case supports their theory, as the function of the pituitary gland in our patient also partially improved after chemotherapy. The infarction-related damage was not irreversible.

## CONCLUSION

In conclusion, we observed a case of IVL with hypopituitarism as a rare complication, which was diagnosed antemortem and successfully treated. Although early chemotherapy is effective, the clinical diagnosis of IVL is challenging. On encountering cases with a variety of symptoms that cannot be explained reasonably, general physicians should consider IVL. Additionally, the mechanisms of lymphoma-associated hypopituitarism associated with IVL have not yet been elucidated, necessitating further case studies and laboratory-based research.

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