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Autopsy Case with Lymphocytic Infundibuloneurohypophysitis as the Contributing Factor

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Abstract

Background: Hypophysitis is a rare, chronic inflammatory disease of the pituitary gland that can lead to pituitary dysfunction. We describe a difficult-to¬-diagnose case of lymphocytic hypophysitis that contributed to death.

Case Report: The deceased was a 70-year-old woman who was by her husband escorted to the toilet because she was unsteady on her feet. Being slumped on the toilet seat and unable to move, she was assisted by her husband who tried but failed to move her. He provided her with water but she died 3 days thereafter. At autopsy, the deceased measured 162 cm and weighed 46.4 kg. The bladder bulged hugely and contained 1450 cc of brown urine. CD20+ and CD3+ lymphocytes infiltrated the posterior lobe of the pituitary gland and severe inflammation, erosion, and fibrin deposition were observed in the bladder mucosa. Biochemical examination disclosed acute renal failure.

Conclusion: Acute renal failure was the direct cause of death. Flaccid neurogenic bladder can cause acute renal failure as a postrenal factor. Lymphocytic infundibuloneurohypophysitis can contribute to flaccid neurogenic bladder. Great awareness of pituitary diseases by forensic pathologists is emphasized.

Keywords: lymphocytic hypophysitis, acute renal failure, neurogenic bladder

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INTRODUCTION

Hypophysitis is a chronic, inflammatory disease of the pituitary gland that can lead to pituitary dysfunction (1). Hypophysitis is still considered a rare condition with an incidence of all its types about 1 in 9 million (2).

In the present study we describe a difficult¬-to-diagnose case of lymphocytic hypophysitis contributing to death.

CASE REPORT

A 70-year-old woman was by her husband (a physician) helped to the toilet because of her unsteady gait. Being slumped on the toilet seat and unable to move, she was assisted by her husband who tried but failed to help her up. He provided her with water, but 3 days thereafter at 6:50 AM confirming that she had no pulse, he contacted the police. The deceased's clothes were wet because of incontinence. Autopsy was performed approximately 30 h after death.

Approximately 1 month before her death, the woman had been admitted to a hospital, complaining of dizziness. A blood test showed a low serum Na level of 127 mEq/L. She was scheduled to undergo a detailed examination for a suspected syndrome of inappropriate antidiuretic hormone secretion (SIADH). On day 4 of admission, and before a confirmed diagnosis, she voluntarily discharged herself claiming a planned vacation.

Autopsy findings

• External findings

The deceased measured 162 cm and weighed 46.4 kg. Rigor mortis was moderate in the joints of the entire body. Livor mortis appeared slightly reddish purple on the back of the body and did not disappear when pressed with the pathologist's fingers. The eyelid conjunctiva was moderately filled, but no extravasation was noted. The lower limbs were edematous.

• Internal findings

The heart weighed 350 g; moderate sclerosis and stenosis of the coronary arteries were noted. No macroscopic lesions were detected in any of the internal organs. Pleural effusion and ascites were not observed. The bladder was markedly bloated, contained 1450 cc of brown urine, and the bladder mucosa appeared red and congested (Fig. 1).

• Histological findings

Lymphocytes infiltrated the posterior lobe of the pituitary gland and the area around cerebral vessels (Fig. 2); CD20+ and CD3+ cells were observed in the posterior lobe, a small amount of CD3+ cells was detected in the anterior lobe, CD20+ and CD3+ cells infiltrated the space around the cerebral blood vessels, and a small number of CD3+ cells infiltrated the cerebral parenchyma. IgG4 immunostaining being negative, IgG4-related disease was ruled out. No granuloma or necrosis was observed in the pituitary gland or the cerebrum.

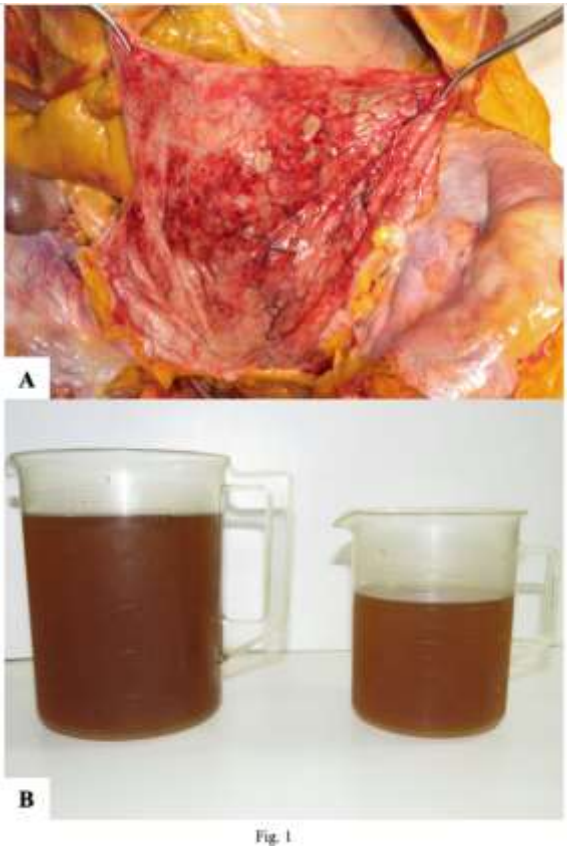

Figure 1. Macroscopic images of the urinary bladder (A) and urine (B).
The bladder bulged hugely, contained 1450 cc of brown urine, and the bladder mucosa looked red and congested.

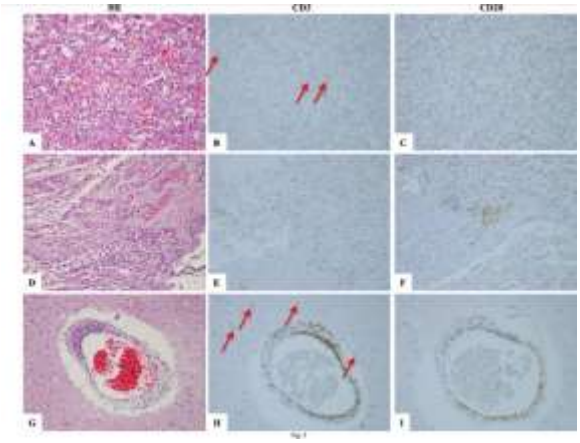

Figure 2. Histological images of the pituitary gland and brain (ABC: anterior lobe of the pituitary gland, DEF: posterior lobe of the pituitary gland, GHI: cerebrum)
Lymphocytes infiltration was noted in the posterior lobe of the pituitary gland and around cerebral vessels. CD20+ and CD3+ cells were observed in the posterior lobe (EF). A small amount of CD3+ cells was detected in the anterior lobe (B, arrows). Infiltration of CD20+ and CD3+ cells was observed around the cerebral blood vessels (GHI). A small number of CD3+ cells had infiltrated the cerebral parenchyma (H, arrows). No granuloma, vasculitis or necrosis was observed.
ADG: Hematoxylin and eosin staining, BEH: immunohistochemistry for CD3, CFI: immunohistochemistry for CD20.

No vasculitis was observed in the pituitary gland or the cerebrum. Renal myoglobin immunostaining was negative. The cerebrum was negative for Congo red. The pituitary lesion was diagnosed as primary lymphocytic infundibuloneurohypophysitis.

The bladder mucosa disclosed severe inflammation, erosion, and fibrin deposition. The liver demonstrated fatty change and loss of cells around the central vein. With the exception of congestion, no other notable findings were detected in other organs.

• Examination Findings

The autopsy revealed the following: plasma renin activity, over 20 ng/mL/hr; uric acid, 21.5 mg/dL; serum Na level, 92.0 mEq/L; serum creatinine level, 7.95 mg/dL; blood urea nitrogen, 146.3 mg/dL; serum cortisol level, 145 μg/dL; and plasma arginine vasopressin (AVP) level, 1.9 pg/mL. SIADH was ruled out by the diagnostic criteria, although the present case was partially similar to this syndrome. Myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA) analysis was negative. Antipituitary cell antibody

was also negative. The urinary myoglobin level was low (10 ng/ml). The reason for the significant increase in serum cortisol, albeit unclear, may have been caused by Predonine tablets (5mg/day) taken by the woman for several days for the treatment of sudden deafness 2 weeks before death.

Based on the autopsy results, the immediate cause of death was attributed to acute renal failure.

DISCUSSION

Hypophysitis, a chronic inflammatory disease of the pituitary gland that can lead to pituitary dysfunction, is classified as primary when the cause is unclear and the inflammation is confined to the pituitary gland, or secondary when the cause is clear and it is a manifestation of systemic disease. It is also induced by drugs such as immune checkpoint inhibitors (1).

Primary hypophysitis is further classified into 3 anatomical subtypes: adenohypophysitis, infundibuloneurohypophysitis, panhypophysitis, and into 6 histological subtypes: lymphocytic, granulomatous, xanthomatous, plasmacytic/IgG4-related, necrotizing, and mixed form (lymphogranulomatous, xanthogranulomatous) (1,2).

Among the six, lymphocytic hypophysitis is the most common. Since a histopathological feature of lymphocytic hypophysitis is lymphocytic infiltration to the pituitary gland, autoimmunity has been implicated in its pathogenesis; thus, lymphocytic hypophysitis is also referred to as autoimmune hypophysitis (1).

According to the location of inflammation in the pituitary gland, primary hypophysitis is classified as follows: lymphocytic adenohypophysitis (LAH), lymphocytic infundibuloneurophypophysitis (LINH), and lymphocytic panhypophysitis (LPH). Whether these three subtypes are completely different diseases, or just different manifestations of the same disease, remains to be established (1).

In LAH, inflammation in the anterior pituitary gland causes partial or complete deficit of anterior pituitary hormones, mainly adrenocorticotropic hormone (ACTH), followed by thyroid-stimulating hormone (TSH), gonadotropins, and prolactin (PRL). LAH is more common in women than in men, and often develops during pregnancy and postpartum. In LINH, which affects males and females equally, inflammation occurs in the posterior pituitary and the stalk, leading to central diabetes insipidus. LINH is thought to be a common cause of what was previously considered idiopathic diabetes insipidus (1). In the present case, diabetes insipidus was ruled out.

In LPH, which is slightly more common in women than in men, but is not associated with pregnancy, inflammation spreads throughout the pituitary gland and causes deficits of both anterior and posterior pituitary hormones (1).

Differential diagnosis of primary hypophysitis is listed as follows: 1.systemic diseases 1) sarcoidosis, 2) granulomatosis with polyangiitis,

3) Langerhans cell histiocytosis, 4) syphilis, 5) tuberculosis, 6) mycoses, 7) IgG4-related disease, 2. sellar and parasellar diseases 1) germinoma, 2)Rathke's cleft cyst, 3) craniopharyngioma, 4) pituitary adenoma, 5) chronic inflammation in parasellar lesions such as paranasal or cavernous sinus (1).

Primary vasculitis of the central nervous system including microscopic polyangitis has been described (3). In the present case, however, no signs of vasculitis were found in any organ, and MPO-ANCA was negative; also, acute renal failure ascribed to flaccid neurogenic bladder was the cause of death. Lymphocytic hypophysitis and cerebral perivascular lymphocytic infiltration were considered contributing factors. Despite various examinations, the cause of perivascular lymphocyte infiltration was not identified.

Forensic autopsy cases involving various pituitary lesions, including hypophysitis, have been reported (4-9). The pituitary gland is often referred to as the master gland, and lesions disturbing its function can result in life-threatening complications and sudden death. The importance of greater awareness of pituitary disease by forensic pathologists is warranted (10). Thus, postmortem examination of the pituitary gland needs to be carried out in all forensic autopsy cases.

Acute renal failure was diagnosed as the direct cause of death in the present case. Flaccid neurogenic bladder can cause acute renal failure as a postrenal factor. Also, inflammatory processes in the pituitary gland may contribute to flaccid neurogenic bladder and may, furthermore, have contributed to the direct cause of death — acute postrenal renal failure.

CONCLUSIONS

Acute renal failure was diagnosed as the direct cause of death. Flaccid neurogenic bladder can cause acute renal failure as a postrenal factor. Lymphocytic infundibuloneurohypophysitis may contribute to flaccid neurogenic bladder.

Acknowledgments

None declared.

Conflict of interest

None declared.

REFERENCES

1. Takagi H, Iwama S, Sugimura Y, Takahashi Y, Oki Y, Akamizu T et al. Diagnosis and treatment of autoimmune and IgG4-related hypophysitis: clinical guidelines of the Japan Endocrine Society. Endocr J in press

2. Joshi MN, Whitelaw BC, Carroll PV. MECHANISMS IN ENDOCRINOLOGY: Hypophysitis: diagnosis and treatment. Eur J Endocrinol 2018;179:R151-63.

3. Salvarani C, Brown RD Jr, Hunder GG. Adult primary central nervous system vasculitis. Lancet 2012;380(9843):767-77.

4. Blisard KS, Pfalzgraf RR, Balko MG. Sudden death due to lymphoplasmacytic hypophysitis. Am J Forensic Med Pathol 1992;13:207-10.

5. Gonzalez-Cuyar LF, Tavora F, Shaw K, Castellani RJ, Dejong JL. Sudden unexpected death in lymphocytic hypophysitis. Am J Forensic Med Pathol 2009;30:61-3.

6. Hatake K, Kubota A, Taniguchi T, Negoro M, Ouchi H, Minami T et al. A case of sudden death of a patient with hypopituitarism. [Article in Japanese] Nihon Hoigaku Zasshi 1994;48:267-73.

7. Kotani H, Abiru H, Miyao M, Kakimoto Y, Kawai C, Ozeki M et al. Pituitary abscess presenting a very rapid progression: report of a fatal case. Am J Forensic Med Pathol 2012;33:280-3.

8. Sun T, Liu L, Sunnassee A, Zhuo L, Zhu S. Sudden death in custody due to pituitary apoplexy during long restriction in a sitting position: a case report and review of the literature. J Forensic Leg Med 2013;20:812-5.

9. Suzuki H, Hayashi K, Fukunaga T. Two forensic autopsy cases of death from unexpected lesions of the pituitary gland. Leg Med (Tokyo) 2014;6:36-9.

10. Wang AR, Gill JR. The Pituitary Gland: An Infrequent but Multifaceted Contributor to Death. Acad Forensic Pathol 2016;6:206-16.