Lymphocytic hypophysitis associated with ovarian hyperstimulation syndrome during assisted fertilization

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ABSTRACT

Lymphocytic hypophysitis is a rare autoimmune disease, often presenting with symptoms of glandular enlargement and endocrine dysfunction. Despite its low prevalence, it remains a significant diagnostic challenge, often requiring tissue biopsy for confirmation. This report describes the case of a 34-year-old woman who developed lymphocytic hypophysitis following ovarian hyperstimulation syndrome (OHSS) during fertility treatment. Initial symptoms included severe headache, uncontrollable vomiting, and behavioral changes. Radiological and neurological evaluations revealed an enlarged pituitary gland with symmetrical hyperintensity on MRI, and laboratory tests showed elevated ACTH and prolactin levels. Further gynecological examination confirmed OHSS. The patient was treated with supportive therapy and high-dose dexamethasone, leading to complete resolution of the symptoms. This case highlights the need for awareness of hypophysitis as a potential complication in women undergoing fertility treatments and suggests the importance of comprehensive diagnostic evaluations to distinguish it from other conditions. Further research is needed to explore any potential link between OHSS and lymphocytic hypophysitis.

KEYWORDS

Lymphocytic hypophysitis, ovarian hyperstimulation syndrome, CSF lymphocytosis.

Introduction

Lymphocytic hypophysitis is a rare autoimmune disease, but the most frequent histopathological subtype of hypophysitis [1,2]. Clinically, it can manifest with symptoms related to glandular enlargement, such as headache and meningism, and/or symptoms of endocrine dysfunction [3]. The prevalence of hypophysitis is low, with an incidence of about 1 in 9 million patients [1], although it is thought to be underestimated [3]. Lymphocytic hypophysitis continues to be a diagnosis of exclusion, with tissue biopsy being the gold standard for a definitive diagnosis [3]. However, clinical, laboratory, and imaging data can assist in diagnosis [4]. Traditionally, lymphocytic hypophysitis has been considered an autoimmune condition that predominantly affects women over men, with an 8:1 ratio [2]. In women, it occurs mainly in the third trimester of pregnancy and in the postpartum period [5]. While other autoimmune diseases are associated in 20-50% of cases [6], it is not typically reported in association with ovarian stimulation [4].

Ovarian hyperstimulation syndrome (OHSS) is characterized by a wide spectrum of clinical and laboratory manifestations caused by the exogenous administration of substances used for the induction of ovulation [7] or, in the assisted reproductive technology (ART) setting, for the induction of multiple follicular growth [8,9]. It is mainly characterized by the displacement of serum from the intravascular space to the third space, primarily to the abdominal cavity. In its severe form, OHSS is life-threatening because it can cause venous or arterial thromboembolic events, including stroke, but clearly not autoimmune diseases [9]. We describe a case of lymphocytic hypophysitis plus OHSS in a young woman undergoing ART procedures.

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Clinical case

A 34-year-old woman was admitted to the Emergency Department (ED) with an around four-day history of worsening headache, associated with uncontrollable vomiting, behavior-

al alterations, and verbal stereotypies. She only repeated "it hurts" while touching her head. Initial clinical and radiological examinations, including CT of the skull and CT angiography of the neck and cerebral vessels, were negative. No fever, leukocytosis, or alterations in other acute-phase reactants were noted in the ED. Neurological evaluation also revealed stiff neck and photo/phonophobia, so she was admitted to the Stroke Unit. An EEG was performed, showing a monomorphic diffuse theta rhythm, suggesting diffuse slowing without epileptic abnormalities. Transcranical Doppler (TCD) was negative. The patient's history was reviewed with family members, who reported the intake of 150 mcg corifollitropin alfa fifteen days earlier, followed by menotropin and ganirelix, in preparation for a fertilization procedure. The patient had been diagnosed with diminished ovarian reserve, and so the family was undergoing medically assisted procreation. Her baseline AMH was 1.8 ng/mL. In the days prior to admission to hospital, during ovarian stimulation, a regular clinical and laboratory check-up had been carried out, with hormone dosage. No drugs had been administered, other than corifollitropin alfa, menotropin and ganirelix. Cabergoline had not been administered. Given this history, pituitary hormone assays were performed, revealing a marked increase in ACTH (487 pg/mL), PRL (79 ng/mL), cortisol (56 mcg/dL), and estradiol (3236 pg/mL). Beta HCG was 2.3 mIU/mL. Lumbar puncture showed an opening pressure of 32 cmH20, pleiocytosis (447 cells/microL), and elevated protein (87 mg/dL). Morphological examination confirmed the presence of lymphocytes only. Since lymphocytic hypophysitis was suspected, brain and pituitary magnetic resonance imaging (MRI) with gadolinium enhancement was performed, showing an enlarged pituitary gland with homogeneous T1 hyperintensity after gadolinium administration (see figure 1). There was no deviation of the pituitary stalk. Subsequently, a complete gynecological evaluation with ultrasound revealed multifollicular ovaries of increased size, measuring 64x38mm on the right and 55x48mm on the left. The ovaries were mobile relative to the surrounding tissues and slightly painful upon movement of the exploratory probe, with a small transonic layer in the Douglas pouch measuring 2.2 cm (see figure 2). A diagnosis of OHSS was made. Blood tests showed leukocytosis (14,000/µL white blood cells), CRP 1.2 mg/dL, hypoalbuminemia (2.7 g/dl), and hemoconcentration. Renal function was normal (eGFR 73 mL/min). After five days in which the patient underwent daily hormonal checks and supportive therapy for OHSS, ACTH and prolactin levels returned to normal values. Supportive therapy included albumin, low molecular weight heparin, and progesterone. Given the evidence of ovarian hyperstimulation associated with a case of lymphocytic hypophysitis, steroid therapy with high doses of dexamethasone (8 mg thrice a day) was administered followed by slow tapering. A week later, the patient displayed complete resolution of the symptoms and a significant clinical improvement.

Discussion

In this case, the diagnosis of hypophysitis was made through clinical, radiological, and laboratory criteria. Gadolinium-enhanced MRI of the pituitary gland is the method of choice and can easily distinguish lymphocytic hypophysitis from a pituitary adenoma. In a pituitary adenoma, MRI shows asymmetrical pituitary enlargement, often with deviation of the pituitary stalk [3]. In lymphocytic hypophysitis, the pituitary gland and stalk are symmetrically enlarged without deviation. MRI shows, as in this case, a homogeneously intense pituitary gland with increased dura [3,4]. Diagnosis is not always straightforward, so

Figure 1 (A) Volumetric increase of the pituitary gland, with a globular appearance and procision of upper profile of the sellar diaphragm. Preserved physiological hyperintensity of the neurohypophysis signal. After gadolinium (B), widespread impregnation of the gland and the peduncle is observed. Pituitary gland is on axis.

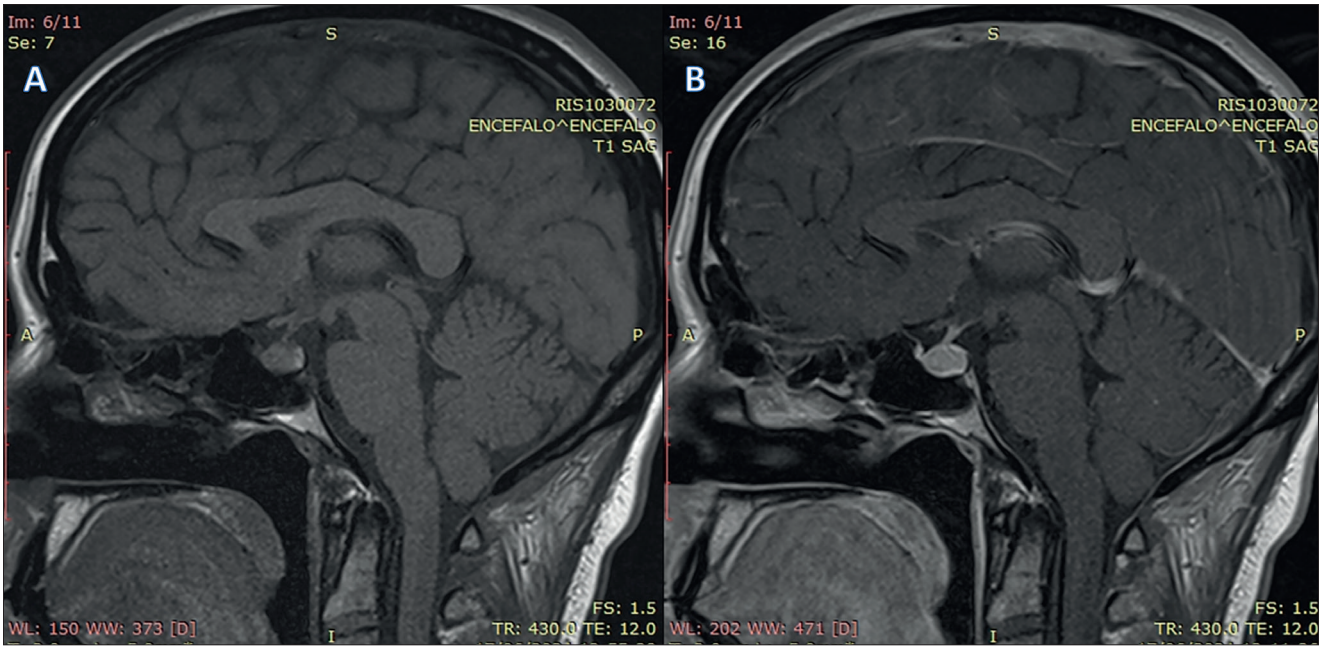
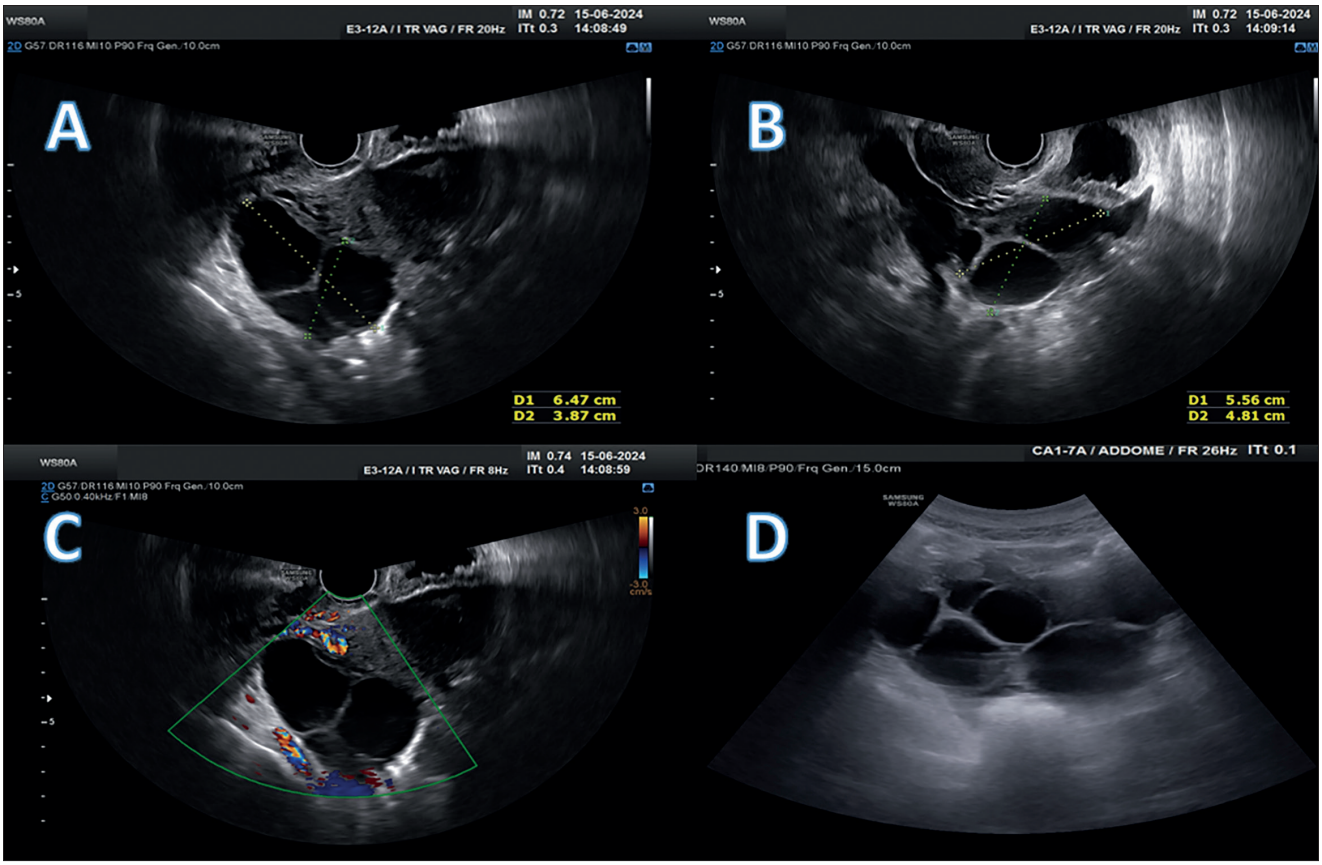


Figure 2 Multifollicular ovaries of increased size, measuring 64x38mm on the right (**A**, **C**) and 55x48mm on the left (**B**, **D**). The ovaries were mobile relative to the surrounding tissues and slightly painful upon movement of the exploratory probe, with a small transonic layer in the Douglas pouch measuring 2.2



a scoring system known as the Gutenberg score has been developed to accurately identify lymphocytic hypophysitis [2]. A total score greater than 1 indicates a pituitary adenoma, while a score of zero or less indicates lymphocytic hypophysitis, with a specificity of 99%, a sensitivity of 92%, and positive and negative predictive values of 97% [2]. In this case, the score was -2. The finding of numerous lymphocytes in cerebrospinal fluid (CSF) examination and elevated blood prolactin and ACTH levels supported this diagnosis. This hormonal profile can be part of an acute hypophysitis clinical picture, where there is an initial increase in PRL and ACTH levels. This is likely related to inflammation, which preferentially affects ACTH- and PRL-secreting cells [10]. Therefore, biopsy of the pituitary gland was not considered, both because of the invasiveness of the procedure in a critically ill patient, and because the clinical and instrumental data were extremely clear. Differential diagnoses were considered; similar CSF findings can occur in HaNDL (headache with neurological deficits and CSF lymphocytosis), but it was excluded due to the presence of meningeal signs and headache preceding neurological worsening [11].

Findings of raised intracranial pressure [12] are also incompatible. No focal neurological signs were found in this patient, so the involvement of a vessel and consequently cerebral ischemia was never suspected [13]. A pituitary adenoma was excluded due to the progressive and spontaneous normalization of hormone levels and the clinical and radiological findings [14]. Neurological symptoms, such as headache and confusion, were completely resolved after steroid therapy, while supportive therapy was administered for ovarian hyperstimulation syndrome as described in the literature [7]. No autoantibodies or involvement of additional glandular structures were documented, reasonably excluding pathologies such as antiphospholipid syndrome, IgG4-related disease, Crohn's disease, and Takayasu's arteritis [15]. It is interesting that while ovarian hyperstimulation syndrome can be related to hormone therapy with exogenous gonadotropins, lymphocytic hypophysitis clearly cannot [15].

Conclusion

Since an association has been described between hypophysitis and physiological hormonal changes in women, we assume that there could also be an association with pharmacological ovarian hyperstimulation. A single case is not decisive, of course, in establishing a causal relationship, but it may represent a starting point for further studies.

References

1. Molitch ME, Gillam MP. Lymphocytic hypophysitis. Horm Res. 2007;68 Suppl 5:145-50.
2. Nanda A, Savardekar AR, Patra DP. Diagnosis and management of

lymphocytic hypophysitis: a synopsis on current perspective. Neurol India. 2018;66(2):405-6.
3. Joshi MN, Whitelaw BC, Carroll PV. Mechanisms in endocrinology: hypophysitis: diagnosis and treatment. Eur J Endocrinol. 2018;179(3):R151-R163.
4. Yuen KCJ, Popovic V, Trainer PJ. New causes of hypophysitis. Best Pract Res Clin Endocrinol Metab. 2019;33(2):101276.
5. Rumana M, Kirmani A, Khursheed N, Besina S, Khalil M. Lymphocytic hypophysitis with normal pituitary function mimicking a pituitary adenoma: a case report and review of literature. Clin Neuropathol. 2010;29(1):26-31.
6. Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. Endocr Rev. 2019;40(1):17-65.
7. Fernández-Sánchez M, Fatemi H, García-Velasco JA, Heiser PW, Daftary GS, Mannaerts B. Incidence and severity of ovarian hyperstimulation syndrome (OHSS) in high responders after gonadotropin-releasing hormone (GnRH) agonist trigger in "freeze-all" approach. Gynecol Endocrinol. 2023;39(1):2205952.
8. Rizk B, Smitz J. Ovarian hyperstimulation syndrome after superovulation using GnRH agonists for IVF and related procedures. Hum Reprod. 1992;7(3):320-7.
9. Mozes M, Bogokowsky H, Antebi E, et al. Thromboembolic phenomena after ovarian stimulation with human gonadotrophins. Lancet. 1965;2(7424):1213-5.
10. Bellastella A, Bizzarro A, Coronella C, Bellastella G, Sinisi AA, De Bellis A. Lymphocytic hypophysitis: a rare or underestimated disease? Eur J Endocrinol. 2003;149(5):363-76.
11. Gómez-Aranda F, Cañadillas F, Martí-Massó JF, et al. Pseudomigraine with temporary neurological symptoms and lymphocytic pleocytosis. A report of 50 cases. Brain. 1997;120 (Pt 7):1105-13.
12. Barbato F, Troise A, Allocca R, Sansone G, Bosso G, Numis FG. Simple detecting of elevated ICP through liquor flow after lumbar puncture. Am J Emerg Med. 2024;75:128-30.
13. Barbato F, Allocca R, Bosso G, Numis FG. Anatomy of cerebral arteries with clinical aspects in patients with ischemic stroke. Anatomia. 2022;1(2):152-69.
14. Rumana M, Kirmani A, Khursheed N, Besina S, Khalil M. Lymphocytic hypophysitis with normal pituitary function mimicking a pituitary adenoma: a case report and review of literature. Clin Neuropathol. 2010;29(1):26-31.
15. Prete A, Salvatori R. Hypophysitis. In: Feingold KR, Anawalt B, Blackman et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000.