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Craniopharyngioma as a Cause of Fever of Unknown Origin

Maria Lagadinou[1], Georgios Markantes[2], Marina Amerali[1], Francesk Mulita[3] Markos Marangos[1], Marina Michalaki[2]

[1]Department of Internal medicine, University Hospital of Patras, Patras Greece
[2]Division of Endocrinology, University Hospital of Patras, Patras, Greece
[3]Department of General Surgery, University Hospital of Patras, Patras, Greece.

Corresponding author:
Maria Lagadinou, University Hopsital of Patras. Petras, Greece. E-mail: m_lagad2004@yahoo.gr

ABSTRACT
Background: Fever of unknown origin is quite common in everyday clinical practice, and the approach is challenging. Prolonged fever as the sole manifestation of craniopharyngioma has been rarely reported in literature. Objective: Herein, we report a case of adamantinomatous craniopharyngioma presented as fever of unknown origin in a 51-year-old woman, initially misdiagnosed as atypical subacute thyroiditis. Case presentation: During the work up, the patient complained about bitemporal hemianopsia. Thus, she underwent a pituitary Magnetic Resonance Imaging, which revealed a mixed mass originating from the pituitary stalk and compressing the optic chiasm. The mass was surgically excised, and the histology confirmed the diagnosis of adamantinomatous craniopharyngioma. The patient remained afebrile post-surgery. We hypothesize that the craniopharyngioma caused an abnormality of thermoregulatory mechanisms due to infiltration of the hypothalamus.
Keywords: fever of unknown origin, craniopharyngioma, PET-CT, treatment.

1. BACKGROUND

Fever of unknown origin (FUO) is defined as a body temperature above 38.3°C on at least two occasions and a duration of illness of ≥3 weeks or having multiple febrile episodes over this time, in which the diagnosis has not been established (1). It has been recorded that no etiology could be determined in 10% to 32% of fever cases (2).

Although most cases of FUO are progressing favorably, about 5% of patients have a final bad prognosis, establishing the importance of cautious differential diagnosis. During the process of etiological diagnosis for FUO, it is significant to carry out a systematic workup following a logical order to promote the diagnosis and treatment (3).

Craniopharyngiomas (CPs) are rare tumors, representing 1 to 3% of all brain tumors in adults (4). They are remnants of Rathke's pouch resulting from malformations of embryonic tissue along the original pathway of the craniopharyngeal duct. Histologically, CPs are classified as adamantinomatous, mostly occurring in children and adolescents, and papillary, mainly occurring in adults. Usually CPs arise from pituitary stalk and compress the optic chiasm, thus causing visual field defects and pituitary insufficiency (5). In a substantial number of patients, headache, nausea, body weight disturbances and depression may occur (6). Also, in 8% of adults cold intolerance is observed, whereas fever has been reported only in a few cases in the literature (5, 6).

2. OBJECTIVE

Herein, we report a case of CP with FUO as the exclusive initial clinical presentation.

3. CASE PRESENTATION

A 51-year-old Greek female was initially referred to the Infectious Diseases Department of the University Hospital of Patras for the investigation of fever up to 39° C and fatigue that had been present for the last two months. Daily fever was the main complaint and arose at any time of the day.

The initial physical examination revealed no remarkable findings. From her past medical history, she had hysterectomy and left oophorectomy when she was 43 years old. The laboratory tests revealed raised erythrocyte

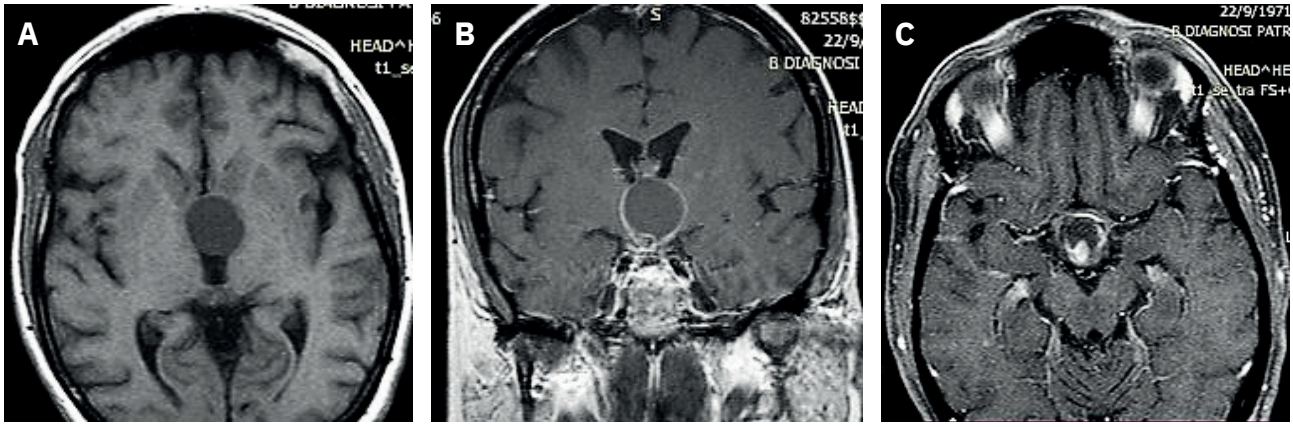

Figure 1 (A-C). Fifty-one-year-old woman who presented with Fever of Unknown Origin and bilateral hemianopsia. Magnetic Resonance Images (MRI) showing the presence of a mixed mass (30mmx24mm) that pushes the optic chiasm. A) Pre-contrast T1-weighted MRIs demonstrate a homogeneously, smoothly outlined mass in the suprasellar cistern, B) and C) Post-contrast T1-weighted MRI demonstrate a large intensely enhancing mixed mass which extends to the hypothalamus.

sedimentation rate (ESR) at 50 mm/hour and C-reactive protein (CRP) at 26 μg/ml (reference range <5μg/dl) as well. All other laboratory tests, blood cultures, echocardiography, chest and abdominal Computed Tomography (CT) scans were normal. Since the initial extensive FUO workup was essentially negative, the patient was then submitted to 18FDG PET/CT scan. The only finding was thyroid gland enlargement with weak 18FDG uptake (SUVmax=3.5). Thyroid parameters were measured (Table 1). Thyroid hormones were within normal range, antibodies against thyroidal peroxiadase (AbTPO) and thyroglobulin were negative while serum TSH was slightly suppressed, which could indicate a previous thyrotoxic phase. Ultrasonography of the thyroid gland showed hypoechogenicity, heterogeneity and reduced blood flow. The constellation of high CRP, mildly elevated ESR, suppressed TSH, enlargement and diffuse uptake to thyroid gland in PET-CT, the sonographic appearance of the thyroid gland and FUO raised the suspicion of subacute thyroiditis (SAT) (de Quervain thyroiditis), even though the thyroid gland was painless. The confirmation of SAT demands very low uptake in thyroid scintigraphy, but due to a recently performed CT scan with IV iodinated contrast media thyroid scintigraphy would be non-diagnostic and therefore was deferred. Based on the above findings, we considered this as a case of atypical SAT or SAT in remission and the patient was treated with methylprednisolone 16 mg twice daily and became afebrile after 3 days. However, during the next few weeks of treatment, the fever relapsed, and the patient started complaining about visual disorders. Ophthalmological examination revealed bitemporal hemianopsia. Thus, the patient underwent a pituitary MRI scan, which showed a large (30mmx24mm) mixed mass of the pituitary stalk that compressed the optic chiasm (Image 1A-C). Endocrine evaluation of the anterior pituitary function pointed out suppressed TSH, low LH and undetectable Estradiol E2 (Table 1). The patient did not complain about polyuria or polydipsia and urine specific gravity was 1011. The mass was surgically excised, and histopathologic examination revealed a typical adamantinomatous CP. After surgery, the patient had panhypopituitarism and diabetes insipidus. She received replacement doses of L-thyroxine, hydrocortisone, and desmopressin (DDAVP). Fever was subsided and the patient remained totally afebrile thereafter.

4. DISCUSSION

This case is an unusual presentation of Fever of Unknown Origin (FUO). In clinical practice, common causes of FUO belong to 4 main etiological categories: infections, neoplasms, noninfectious inflammatory diseases (e.g. connective tissue diseases, vasculitis), and miscellaneous conditions (3). This patient underwent a thorough investigation for the cause of fever. Physical examination revealed no remarkable findings. Laboratory and imaging exams showed increased inflammatory markers as well as diffuse week thyroid 18FDG uptake on PET/CT scan. Incidentally discovered diffuse 18F-FDG thyroid uptake occurred in 1-2,9% of patients who underwent PET/CT scans and is associated with thyroid dysfunction, chronic lymphocytic thyroiditis, or metastatic disease (7-9). SAT is rarely presented as diffuse or focal 18F-FDG uptake (10, 11). SAT is inflammatory destructive thyroiditis that occurs 1-3 months post upper respiratory tract viral infections and is sometimes a cause of FUO because of its atypical presentation (12). SAT has a triphasic clinical course. In the initial inflammatory phase, painful thyroid gland, fever up to 39.5° C, symptoms of thyrotoxicosis and raised inflammatory markers predominate. However, in 5% of patients, palpation of thyroid gland is painless (12, 13). Also, painless SAT has been described during or up to 168 days from the onset of COVID-19 symptoms (14, 15). Thus, in the era of COVID-19 pandemic, though our patient had no documented COVID-19 illness, the inability to find another cause for the patient's fever, we misdiagnosed her as SAT. Despite that, during the work up, because of the patient's complaint about bitemporal hemianopsia, she underwent a pituitary MRI which revealed a large pituitary stalk mass, leading us to the final diagnosis. It was noteworthy that brain did not have increased 18F-FDG uptake on PET/CT scan. Generally, the use of 18F-FDG PET/CT scan is limited to the evaluation of brain tumors

Variable	7/9/2022	29/9/2022
TSH **R.V: 0,4-4,2 μIU/mL**	0.374	0.155
T3 R.V: 0,8-2,0 ng/ml	0.92	———
T4 **R.V: 5,1-14,1 μg/dl**	9	———
fT4 R.V:0.8-2.0 ng/dl	——-	1.18
TG R.V: 3,5-77ng/ml	6.5	11.19
Anti-TG R.V: <115 IU/ml	23.3	———
Anti-TPO R.V:<34IU/ml	15	
FSH R.V: 1,5-12.4 mIU/ml	——-	16.9
LH R.V: 1,5-9.3mIU/ml	——-	2.7
Prolactin R.V: 4.79-23.3 ng/ml	——-	20.5
E2 Estradiol pg/ml	——-	<5.00
Testosterone R.V: 2.6-43.2 ng/dl	——-	<2.50

Table 1. Endocrine evaluation of patient at initial presentation to the endocrine division (7/9/2022) and at the diagnosis of CP (29/9/2022) Abreviations: R.V: reference value, TSH: thyroxin stimulating hormone,T3: triiodothyronine, fT3: free T3, T4: thyroxin, fT4: free T4, TG: Thyreoglobulin, anti-TG: Antithyroglobulin antibody, anti-TPO: thyroid peroxidase antibodies, FSH: Follicle-Stimulating hormone, LH: Lutenizing hormone

because of the high basal activity of the cerebral cortex and grey matter (16). The inappropriately low serum LH levels in the face of undetectable estrogen indicates partial hypopituitarism. That finding was missed in her initial evaluation because her premature amenorrhea was attributed to the hysterectomy. We did not measure ACTH and cortisol because she was treated with methylprednisolone wrongly for SAT. Also, the 2ndsuppressed TSH with normal thyroid hormones could was rendered to the glucocorticoid treatment. It is known that glucocorticoids inhibit TSH secretion (17, 18). The mass was surgically excised, and histology confirmed the diagnosis of adamantinomatous CP.

To the best of our knowledge this is the first report of CP causing persistent fever as the initial and sole symptom in an adult patient. As far as we know, only a few cases of CP associated with fever have been reported. Krueger David W. et al reported a case of a 73-year-old male rancher who was evaluated for FUO and a cyclic leaking craniopharyngioma was found to be the source of recurrent fever, meningismus, and coma (7). Moreover, hypothalamic syndrome may be suspected, when disruptions in body temperature regulation, growth, and water balance or eating behavior disorders are present (5). Rangel et al reported a case of a 19-year-old boy who was admitted to the hospital with a 4-day history of acute severe headache after strenuous physical exercise followed by altered sensorium, fever, and neck stiffness and was diagnosed with aseptic meningitis due to spontaneous rupture of a multicystic CP (6). Madhumita N. and Rakesh K. M. reported an unusual case of a ten years old boy diagnosed with craniopharyngioma and hypopituitarism presenting with prolonged fever (8).

Generally, CP can cause prolonged or recurrent fever due to various reasons (19). It can be due to abscess of the cystic portion of the mass, infection of the Rathke's cleft cyst, associated abnormality of hypothalamic thermoregulatory mechanism, leaking craniopharyngioma causing aseptic meningitis or other associated infections (20). In our case, the cause of the fever probably was the disruption of the thermoregulatory mechanisms due to hypothalamic infiltration by the tumor.

5. CONCLUSION

In conclusion, this is the first case of adamantinomatous CP presenting with FUO as initial and unique manifestation in a menopausal woman. It demonstrates that CP should be listed as a cause of fever of unknown origin. Also, incidentally discovered thyroid 18F-FDG uptake on PET/CT scan should interpret with caution.

- **Consent for publication:** We had the patient's consent to publish the case study
- **Author's contribution:** M.L. collected patient's data and wrote the manuscript, M.A., G.M., T.P., C.M. collected patient's data, Mar. Mix. wrote and revised the manuscript, and M.M. revised and approved the manuscript.
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