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CASE REPORTS

PAPILLARY THYROID CARCINOMA AND FEVER OF UNKNOWN ORIGIN - CAUSALITY OR COINCIDENCE?

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ABSTRACT

Papillary thyroid carcinoma is a common and usually asymptomatic tumor. Some reports questioned a possible association between febrile syndromes and papillary carcinoma. The authors report a 17-year-old female with fever of unknown origin for 3 months, constitutional symptoms and markedly elevated inflammatory markers. An exhaustive diagnostic work-up led to the diagnosis of papillary thyroid cancer. The patient underwent total thyroidectomy and radioiodine therapy, remaining asymptomatic after two years of follow-up. We aim to discuss a possible causal link between a prolonged fever and papillary thyroid carcinoma, previously described and highlight the importance of remembering solid tumors in the investigation of prolonged fever of unknown origin.

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Case Report

Fever of unknown origin is a challenging entity and although it mostly represents a sign of infection, it can also have oncologic origin.[1] Neoplastic fever is mostly associated with hematopoietic malignancy, whereas this association with solid endocrinologic tumors is rarely described.[1,2,3,4,5] Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer and usually presents as an asymptomatic nodule.[4] There are sparse reports questioning a possible causal link between febrile syndromes and papillary carcinoma.[3,4] The authors report a case of PTC diagnosed coincidently with fever of unknown origin.

A 17-year-old female presented to the pediatric emergency department with fever (up to 39.7ºCelsius), hypersudoresis, chills, fatigue and generalized weakness associated with gastrointestinal symptoms (diarrhea, vomiting and abdominal pain). On physical examination she was hypotensive (92/51 mmHg), febrile, pale and with abdominal tenderness. Examination of the lymph nodes, heart and lungs was unremarkable. Laboratory tests showed elevated levels of C-reactive protein (210.06 mg/L; normal range 0-5 mg/L) and erythrocyte sedimentation rate (>120 mm/h), with normal range of white blood cell count ($9.48x10^9$/L; normal range 4.5 – $13.5x10^9$/L). Hemoglobin and peripheral blood smear were normal. Abdominal ultrasound revealed hepatosplenomegaly (17 cm and 13.8 cm) and mesenteric adenomegalies. The patient was admitted and empiric intravenous antibioterapy was started (Ceftriaxone 4 g twice daily) for presumptive diagnosis of infectious colitis. Symptoms persisted after treatment and so etiological investigation proceeded.

An extended infectious, immunologic and rheumatologic investigation was also performed and showed no relevant results (Table 1 and 2).

At the same time, an intensive imaging and endoscopic work up including chest radiograph, whole-body CT, echocardiography, PET-FDG, upper digestive endoscopy and bronchofibroscopy was performed and showed polyserositis (pleural, pericardial, splenic effusion). Generalized lymphadenopathies (cervical, axillar, mesenteric and retroperitoneal) were also encountered.

For three months multiple cycles of broad-spectrum antibiotics and non-steroidal anti-inflammatory drugs were performed, with no clinical response.

A fine needle aspiration (FNA) biopsy of a retroperitoneal lymph node was performed, with the histology showing only reactive alterations. Myelogram was normal and bone marrow biopsy revealed a lymphocytic infiltrate, without evidence of lymphoproliferative disease.

By that time a supraclavicular lymph node was detected on the physical examination. It motivated a cervical ultrasound that revealed, a 19 mm sized solid mass on the thyroid isthmus, hypoechoic. It also objectified cervical and supraclavicular lymph node enlargement with loss of hilum differentiation. The thyroid function (thyroid-stimulating hormone 1.17 uUI/mL - normal range 0.27-4.2 uUI/mL; thyroxine 16.47 pmol/L - normal range 11.97-21.88 pmol/L) and serum thyroglobulin (2.60 µg/L; normal range 3.5-77 µg/L) were normal. An excisional biopsy of two cervical ganglia showed no abnormalities. The investigation proceeded and a FNA biopsy of the thyroid nodule led to diagnosis of papillary thyroid carcinoma.

The PET was repeated and showed no abnormal

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Table 1. Imunologic workup.

Imunoglobulin G	**Elevated (20.5 g/L; normal range 6.8-14.5 g/L)**
Imunoglobulin A, M, E	Normal
Imunoglobulin G subclasses	Normal
Light chains	**Elevated**
kappa light chain	Elevated (4.85 g/L; normal range 2-4.4 g/L)
lambda light chain	Elevated (3.19 g/L; normal range 1.1-2.4 g/L)
kappa/lambda	Normal
C3	**Elevated** (1.83 g/L; normal range 0.75-1.35 g/L)
C4	Normal
RF, ANA, ANCA, Anti-transglutaminase IgA, Anti-streptolysin-O, Anti-smooth muscle, Anti F-actin, Anti-Sm Anti-RNP, Anti SS-A/B, Anti-cardiolipin IgM/IgG, Anti-B2GPI IgM/IgG, Anti-thyroglobulin, Anti-thyroid peroxidase, Anti-GBM, HLA-B27, Anti-hepatic antigens antibodies	Normal

Table 2. Microbiologic investigation.

Serologies: Toxoplasmosis, Herpes simplex I/II, Borrelia, Brucella, Parvovirus B19, EBV, CMV, Chlamydia, VDRL, Legionella, Coxiella Burnetti, Leismania donovani, Listeria, Leptospira, Bartonella, Widal reaction, Rose Bengal reaction, HBV, HIV I/II, HCV, HAV	Negative
Respiratory viruses and atypical bacteria on nasopharyngeal secretions (PCR)	Negative
Serial blood, urine and feces cultures	Negative

uptake in the tumor. Chromogranin A was normal (2.3 nmol/L, normal range 0.55-2.76 nmol/L). FNA biopsy of the supraclavicular ganglion didn't reveal carcinoma invasion, immunohistochemistry for thyroid transcription factor-1 and thyroglobulin were normal. The patient underwent total thyroidectomy and level V lymph node excisional biopsy. Macroscopically there was an isthmic nodule (1.2 cm x 1 cm) that presented the typical microscopic features of classic papillary thyroid carcinoma. Two V level compartment lymph nodes were positive for metastasis. The anatomopathological exam revealed a pT1bN1b R0 staging, which corresponds to a stage I and radioiodine therapy was the next step.

Seven days before thyroidectomy the patient reached apyrexia and an improvement of the inflammatory markers was documented (PCR 25.70 mg/L), sustained post-surgically. After two years of follow-up the patient remains asymptomatic, without evidence of structural or biochemical disease.

Discussion

The authors hypothesize whether the symptoms observed in this patient were of paraneoplastic origin, manifested as a systemic auto-inflammatory syndrome of unknown etiology.

It is known that papillary thyroid cancer is usually asymptomatic; however, there have been some clinical reports of paraneoplastic syndromes associated with this tumor, such as cerebellar syndrome, dermatomyositis, syndrome of inappropriate antidiuresis and Guillain-Barré syndrome.[6,7,8,9]

There are rare reports in the literature of fever and systemic manifestations in patients with PTC.[3,4] Our patient presents with many coincident clinical features with this described cases, such as prolonged fever, lymphadenopathy, hepato-splenomegaly, fatigue, general weakness and serositis.[3,4,10]

Considering the high incidence of this tumor there is an increasing chance of coincidental findings and misinterpreted associations. However, it is remarkable that no alternative diagnosis was found after three months of exhaustive investigation and the patient remains asymptomatic two years after the diagnosis.

In a patient with non-explained systemic and constitutional symptoms efforts must be made to exclude not only lymphoproliferative disease but also solid tumors, with thorough investigation and biopsy of all the suspect lesions.

This patient has a favorable prognosis given the young age of diagnosis and stage 1 thyroid cancer. In conclusion, this report highlights a probable paraneoplastic presentation of papillary thyroid

carcinoma. In a patient with non-explained constitutional symptoms malignancy must be ruled out with thorough investigation and biopsy of all the suspect lesions.

Compliance with Ethical Standards

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Conflict of Interest: None

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