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Case Report: Chronic urticaria associated with lung adenocarcinoma: a paraneoplastic manifestation? Case report and Review of the literature.

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Point-by-point response to reviewers and editor.

The authors of this manuscript wish to thank the editor and the reviewers for their helpful comments. We consider that this new revised version is certainly improved, given the constructive nature of the observations. This is our point-by-point response:

Reviewer #1:

Specific Comments to Authors: The authors describe a case of urticaria associated with adenocarcinoma, but there is still room for clarification.

Query 1: The article describes the high expression of TTF-1 (thyroid nuclear factor 1) in lung tissue and its relationship with lung cancer. It seems that it has little relationship with urticaria?

Response:

We fully agree with Reviewer 1 and therefore, we proceed to explain the subject:

Thyroid transcription factor-1 (TTF-1), also known as NKx2.1 or thyroid-specific enhancer-binding protein, is a member of the NKx2 family of tissue-specific transcription factors which is expressed in the thyroid follicle, parathyroid gland, alveolar epithelium, and the diencephalon, which originate as well in the ectoderm, and participates in the differentiation, development and functional maintenance of the aforementioned organs (1). It is currently considered the best molecular marker for the differential diagnosis of thyroid and lung tumors (2,3). In the thyroid gland, TTF-1 participates in the expression of genes related to the differentiation of thyroid follicular cells and the synthesis of their products, Thyroglobulin (TG), Thyroid Peroxidase (TPO) and Thyrotropin Receptor (TSHR). Most patients with chronic spontaneous urticaria present with thyroid disorders (approximately 54%), with epidemiological data that vary from one population to another (4), with subclinical hypothyroidism being one of the most frequent presentations. Autoimmune disease at the level of the thyroid gland has also been documented in patients with Chronic spontaneous urticaria (CUS), being one of the mechanisms underlying the subclinical hypothyroidism observed in a large proportion of

patients (5). The infiltration of the gland by autoreactive T lymphocytes and B lymphocytes against thyroid antigens (TG, TPO and TSHR) improve the synthesis of IgG or IgE antithyroid autoantibodies, as documented by current scientific evidence (6,7). The presence of antithyroid autoantibodies is strongly related to CSU with rates $\geq 10\%$ (5). IgG autoantibodies against TPO are more frequent in CSU than the other reported antithyroid autoantibodies (8). It has been shown that in patients with positive antithyroid autoantibodies, whether anti-TPO or anti-TG, these have the property of degranulating mast cells by themselves, leading to the release of proinflammatory mediators such as histamine, chymase, tryptase, leukotrienes, prostaglandins, among others. others, closely related to the pathophysiology of CSU (6-8).

We have added the following information in the discussion (highlighted in green):

Larenas-Linnemann et al carried out an extensive review of the literature (26 cases in total), in which they argue that chronic urticaria can be caused by cancer and that it can resolve with its cure (9). The most frequent type of cancer was carcinoma (17 of 25, 68%), and only 24% were of hematological origin, one seminoma and one astrocytoma. 24% of the cases were papillary carcinomas of the thyroid gland. After treatment with chemotherapy or tumor resection, the urticaria resolved in all patients.

Based on the foregoing analysis, we could infer that the high expression of TTF-1 in lung carcinomas would be conditioning the increased expression of TG, TPO and TSHR at the thyroid level, which would disrupt the mechanisms of glandular immune tolerance leading to an autoimmune response characterized by the synthesis of AAbs; which in turn degranulate mast cells, conditioning the clinical appearance of wheals and itching, as has been documented in this paper. However, we consider that several studies are still necessary to establish a causal relationship between chronic urticaria and malignancy. Especially in those patients where there is no evidence of thyroid pathologies.

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Query 2: There is no direct evidence in the article to support that urticaria is related to lung cancer, urticaria or skin changes caused by lymphoma are more, and there is no skin pathological support?

Response: Unfortunately, we do not have skin pathological support.

Query 3: There is no image of enhanced chest CT in the patient data?

Response: Yes, we show the chest computed tomography (CT) of the patient in the figure 4.

Query 4: Are there any abnormalities in the patient's blood tumor indicators, and are there any correlations with urticaria?

Response: We clarify in the discussion: "There were no abnormalities in the requested tumor markers in the patient. After an extensive literature search in different databases, no relationship was found between elevation of tumor markers

and the appearance of urticaria” highlighted in green. The tumor marker levels are presented in table 2 in the case report.

The English was edited. Changes are highlighted in yellow

Reviewer #2:

Query 1: the discussion should be improved and compare your result with other studies.

Response: We fully agree with Reviewer 1 and therefore we improved the discussion and compared our results with other studies.

Paraneoplastic syndromes are commonly associated with lung cancer, it has been reported in approximately 10% of cases of this type of cancer (1). Urticarial lesions (hives or wheals) that are commonly accompanied with severe itching, have been considered a potential paraneoplastic dermatoses present in patients with internal malignancy. Hives with chronological activity greater than 6 weeks (chronic urticaria), with also an unknown cause (spontaneous) and with poor response to treatment with antihistamines and corticosteroids (2,3) have been associate with these episodes. The term malignant urticaria has emerged in recent years and it is defined as a paraneoplastic manifestation that meets the Curth criteria, where the urticarial lesions develop only after the clinical presentation of the malignant tumor or follow a parallel course to the development of the malignant tumor. The complete disappearance of the cancer results in the disappearance of the dermatosis and the recurrence of the cancer causes reappearance of the dermatosis (4). The scientific evidence may vary with different results in one population and another, and few cases has been documented in the specialized literature.

The first report dates back to 1942, Urbach et al described a case of chronic urticaria associated with rectal carcinoma. The dermatological lesions resolved after surgical removal of the carcinoma and suggested a causal relationship between chronic urticaria and neoplasms (11). Since then, several cases of urticaria related to malignant neoplasms have been described. Hills et al in 1968, followed by Conget et al in 1987, in the city of Barcelona. Both works were pioneers in establishing the potential association between chronic urticaria and lung adenocarcinoma (5,6). Other lung cancers have also reported accompanying chronic urticaria. De et al reported a case of chronic urticaria in a 57-year-old farmer, diagnosed with large cell undifferentiated lung carcinoma, with no family history of malignancy and no history of allergies (7). They report that the patient received management with antihistamines, oral corticosteroids, topical corticosteroids and emollients for more than 4 years, without resolution of the clinical picture. The patient presented pleuritic pain on the right side, the chest X-

ray revealed a prominent hilum and atelectasis in the right lower lobe. Subsequently, chest CT confirmed a soft tissue mass in the right mainstem bronchus causing collapse of the ipsilateral lower lobe (T4N2M0). Endobronchial histology confirmed a large cell undifferentiated carcinoma. He was treated with palliative high-dose external beam radiotherapy (39 Gray in 13 fractions), with significant resolution of the urticaria. After one year, the dermatological lesions reappeared, the imaging findings showed reappearance of the tumor with involvement of the superior vena cava. He received antineoplastic management with chemotherapy "Mitomycin + Ifosamide + Tixplatin", with significant resolution of the tumor and urticarial lesions. The researchers reported that ten months after the start of chemotherapy, the patient died from complications associated with brain metastases. In our case report, the patient, in addition to wheals and itching, presented respiratory symptoms, which led to an exhaustive clinical examination with radiographic and tomographic findings of the pulmonary nodule described. The symptoms also resolved with the initiation of anti-neoplastic treatment.

We have added the following information in the discussion (highlighted in green):

Greiner et al reported the case of a 56-year-old patient, with no history of atopy or allergic diseases, who presented with urticarial dermatological lesions associated with small cell lung carcinoma (8). The researchers reported that the urticaria was refractory to treatment with intravenous corticosteroids + second-generation antihistamines. The symptoms resolved completely with a higher dose of corticosteroids (methylprednisolone) and surgical intervention for the lung carcinoma. Following tumor removal, the symptoms of urticaria resolved significantly.

Another case report in which urticarial lesions resolve completely with antineoplastic treatment (surgical and/or pharmacological), was the work carried out by Campanelli et al (9). They reported a case of chronic urticaria as a paraneoplastic manifestation in a patient with colon adenocarcinoma with no family history of cancer and atopy. After surgical treatment, left hemicolectomy, plus adjuvant chemotherapy x 5 weeks, the urticaria completely disappeared. Follow-up of the case thirteen months after completion of antineoplastic treatment showed complete resolution of cancer and urticaria. Clinical scenario very similar to that evidenced in our report. The patient reported that the dermatological lesions (wheals and itching) resolved with the antineoplastic treatment received.

Larenas-Linnemann et al, carried out a case report and an extensive review of the literature (26 cases in total), where they argue that chronic urticaria can be caused by cancer and that it can resolve with its cure (12). In the letter to the editor published in the journal Allergy (2018), they reported the case of chronic

recalcitrant urticaria that preceded the diagnosis of Hodgkin's lymphoma in a 31-year-old patient. They report that the symptoms did not resolve with treatment with second-generation antihistamines (levocetirizine 3X the usual dose) and that the symptoms only temporarily ameliorated with oral corticosteroids. They report that the symptoms exacerbated during the first two chemotherapy sessions, with complete resolution after the third antineoplastic treatment session. They note that the patient has been in remission for 7 years and the hives have not returned.

In the same work, of the 26 cases studied, 77% presented chronic urticaria with poor response to treatment with antihistamines, requiring oral corticosteroids to control symptoms. Most of the patients (15/22) had presented urticaria between 2 – 8 months before the diagnosis of malignancy. The most frequent type of cancer was carcinoma (17 of 25, 68%), and only 24% were of hematological origin, one seminoma and one astrocytoma. 24% of the cases were papillary carcinomas of the thyroid gland (12). In 19/25 cases, the neoplasm was detected in an early and asymptomatic phase; the researchers argue that the early diagnosis was due to the exhaustive approach of the treating physicians in search of the cause of the urticaria. After treatment with chemotherapy or tumor resection, the urticaria resolved in all patients.

In a retrospective population-based cohort study from Taiwan, Chen et al demonstrated that patients with chronic urticaria have a 2.2 (95% CI, 2.0-2.3) increased standardized incidence (SIR) of developing cancer, especially hematologic malignancy (SIR=4.1; 3.1-5.4) and non-Hodgkin's lymphoma (SIR=4.4, 95% CI, 3.0-6.1). Of a total of 12,720 patients with chronic urticaria, treated with antihistamines and without a history of malignant tumors, autoimmune diseases, atopy or allergic diseases; there were 704 cancers among the patients studied, with hematological neoplasms being the most observed (10). Despite these findings, the 2017 review and update of the EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis, and treatment of urticaria (13), states that there is insufficient evidence of a Causal correlation of urticaria with neoplastic diseases to support routine screening for malignancy in diagnosing underlying causes of urticaria. Therefore, more studies are necessary to contribute to the scientific evidence that supports the potential relationship between chronic urticaria and malignancy. Our proposal aims to provide new knowledge that enriches the available scientific literature and that serves as a foundation for the construction of future works that allow establishing the potential causal relationship between chronic urticaria and cancer.

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Query 2: Please note the patients past drug history.

Response: The patient does not have past drug history. This is clarified in the “History of past illness” in the section of “case presentation”

The English was edited. Changes are highlighted in yellow

EDITORIAL OFFICE'S COMMENTS

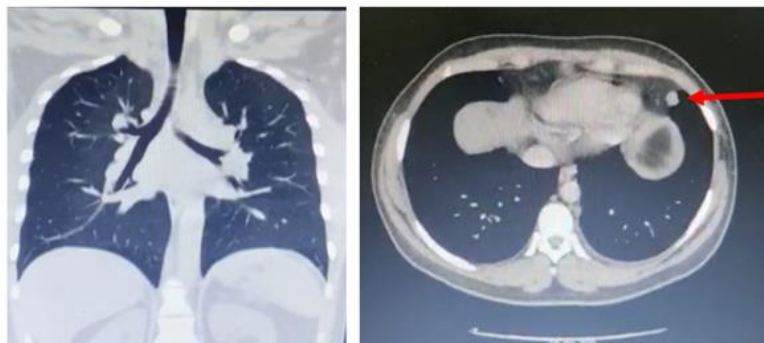
(1) *Science editor:*

Query 1: This manuscript reported a case of urticaria associated with adenocarcinoma. There is no direct evidence to support the relationship between urticaria and lung cancer, lack of skin pathological pictures, chest CT enhanced images and patients' blood tumor index levels, please supplement and modify.

1. In the literature there is no direct association between urticaria and lung cancer. Urticaria as a cutaneous paraneoplastic syndrome is considered a controversial association as previously explained, however in this case the appearance of urticarial lesions coincided with the diagnosis of the lung tumor and in turn remitted once treatment was started, which could be considered to be meets Curth's Criteria so that association can be established.
2. Photographs of the skin lesions presented by the patient are attached (Figure 2 in the case report).



3. Chest tomography image with evidence of pulmonary nodule is attached (Figure 4 in the case report).



4. Result of tumor marker levels: no alteration was found within the requested tumor markers in the patient. The results are shown below and the table 2 in the case report.

Variable	Result	Reference values
Alpha fetoprotein	0,50	54,8 U/L
Carcinoembryonic Antigen	1,02	0-3 U/L
CA 19-9	31	0-37 U/L

Response:

Query 2: In the discussion section, please add an explanation of the innovation of this study compared with previous studies.

Response: We added an explanation in discussion section (highlighted in green):
This case report provides new knowledge that enriches the available scientific literature and that serves as a foundation for the construction of future works that allow evaluation of a potential causal relationship between chronic urticaria and cancer.

The English was edited. Changes are highlighted in yellow

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted.

I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Query 1: Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, “Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...”.

Response: The figure legends were changed and edited according to the editor notes.

Query 2: Please provide the original figure documents.

Response: Original images are attached to the manuscript document.

Query 3: Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response: A power point document is given to ensure the reprocessing by the editor.

Query 4: In order to respect and protect the author’s intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is ‘original’, the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Response: A power point document is given to ensure the reprocessing by the editor at bottom right side of each slide the Copyright ©The Author(s) 2022 note is pointed.

The English was edited. Changes are highlighted in yellow