

Paraneoplastic Eosinophilia: Report of 2 Cases

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Abstract

Introduction: Eosinophilia is associated to parasitic infections, allergy, collagen-vascular and hypersensitivity diseases, while Paraneoplastic Eosinophilia is an infrequent finding associated to hematologic or solid tumors¹. The physiopathological mechanism is not fully understood, despite the involvement of several growth factors.

Presentation of Case: The authors present two cases of paraneoplastic eosinophilic disease: in the first case, a 52 year-old man with history of sudden onset dyspnea, weight loss and asthenia. The chest Roëntnography showed opacity in the lower two-thirds of the right hemithorax and the blood work showed an eosinophilia of 14.300/microL (AC). The patient was admitted and performed all possible diagnostic workup, without direct signs of tumor. Despite the absence of neoplastic definitive diagnostic, the eosinophilia increased to 18.800/microL (AC), chemotherapy was considered, however after unfavorable clinical development the patient died after 31 days of hospital admission.

The other patient, a 60 year-old man with previous diagnostic and treatment of a colonic adenocarcinoma, clinically stable and without evidence of disease progression, was found evidence in a control bloodwork an eosinophilia of 4800/microL (AC). Despite discarded other causes of eosinophilia causes, was found evidence of neoplastic recurrence. The patient was eligible for chemotherapy, the eosinophilia was oscillating during all the treatment, suspended by the 3rd cycle due to clinical deterioration. The patient died 2 weeks after treatment discontinuation.

Conclusion: Eosinophilia secondary to solid tumors is a rare finding but usually is a sign of advanced neoplastic disease or progression of a previous condition, with poor prognosis at the time of diagnostic.

Keywords: Paraneoplastic; Eosinophilia; Solid Tumor; Prognosis

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Consent: Consent was taken from the patient's next of kin for publication of this case report.

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Introduction

Peripheral blood eosinophilia include allergic, infectious and neoplastic disorders as main causes; the goal in the initial evaluation is to identify the ones that require specific treatments, such as the parasitic infection, drug hypersensitivity, leukemia and non-hematologic cancer^[4]. The definition of eosinophilia considers an absolute count above 500 eosinophils/microL and the degree of eosinophilia can also be categorized as mild (500 to 1500 eosinophils/microL), moderate (1500 to 5000 eosinophils/microL) or severe (>5000 eosinophils/microL); the concept of hypereosinophilia (HE) includes the moderate-severe range (*ie*, ≥ 1500 eosinophils/microL) and do not require the presence of end-organ manifestations^[5].

Paraneoplastic eosinophilia (PE), however, represents a subset of secondary eosinophilia in which are involved tumor production of eosinophil growth factors such as interleukin IL-3, IL-5, and GM-CSF^[3,5]. The specific role of these mediators is still to be understood when the neoplastic etiology is considered.

It is also important to differentiate PE from primary eosinophilia, typical of the hematological practice since it represents a clonal phenomenon induced directly by the hematologic neoplastic process^[6].

PE is scarcely described in the literature, mostly associated to neoplastic disease in advanced state and virtually possible in all tumor types.

Case Presentation

Case 1. Patient of 52 years-old, male, with mild smoking habits and past history of type 2 Diabetes Mellitus, Hypertension, observed in the Emergency Service (ER) with history of sudden onset dyspnea, with no other respiratory symptoms. The oximetry was 95% (atmospheric air) and the rest of the vitals were normal. The patient reported a history of weight loss of 7 Kg in the last five months, asthenic and progressively incapacitated to perform his work tasks (bus driver). Two months before the ER episode, the family practice doctor assumed the patient was depressed and medicated him with escitalopram 20mg id, without benefit.

In the physical examination the patient was pale, hydrated, with no signs of cyanosis or jaundice, always with shortness of breath while observed; in the pulmonary auscultation the most evident feature was the diminished murmur in the lower two-thirds of the right hemithorax. The other pulmonary areas were normal. There were no palpable ganglia, no visceral enlargement and no distal oedema.

The arterial blood gas analysis was normal and the analytical work-up showed a blood count with Hemoglobin and platelets within the normal range and a hyperleucocytosis of $43.38 \times 10^9/L$ with eosinophilia of 14.300/microL (AC), confirmed in the blood smear analysis. There were no changes in the kidney, ions levels and liver function tests.

The thoracic X-ray showed an opacity in upper two-thirds of the right hemithorax and the patient ended up being admitted for etiologic study. The patient underwent a thoracic ultrasound that showed a loculated pleural effusion; the thoracic CT-Scan put to evidence lung atelectasis, mediastinal left deviation, evidence of mediastinal ganglia and no signs of direct pulmonary or pleural lesions. The abdominal and pelvic Ct-scan was normal. By the 9th day of admission, the patient was already O2 dependent and very symptomatic. A diagnostic thoracentesis was performed, with serohematic liquid categorized as an exudate and an anatomopathologic analysis highly suspicious of presence of neoplastic cells (increased nucleus/cytoplasm ratio and prominent nucleolus). The Bronchofibroscopy

didn't show any direct signs of tumor and the Bronchoalveolar Lavage Fluid retrieved no abnormal results. The roentnographic evolution of the patient is shown in sequence, where the images are concordant with the clinical decline of the patient during the hospital stay (Figure 1). Performing a myelogram was considered, but decided against considering the growing respiratory decompensation periods.

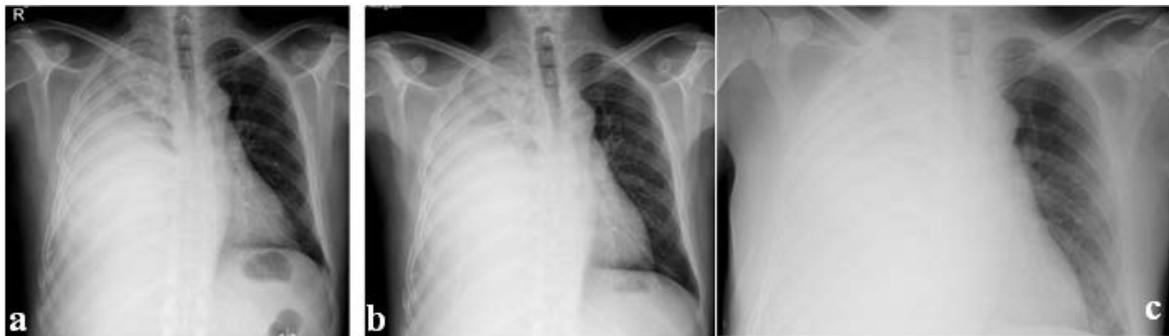


Figure 1 Imagiological evolution in the patient, **a.** Chest X-ray at admission showing a vast opacity in the right hemithorax, with few lung available to ventilate. **b.** 5 days after admission, no imagiological improvement. **c.** After performing thoracentesis (9 days after admission), with further clinical deterioration.

Faced with no definite neoplastic diagnostic and a progressive clinical decline, the patient was discussed in multidisciplinary reunion and decided to start chemotherapy admitting the tumor would most likely be a primary, pulmonary lesion undetected in the exams made, only supported by the mild suggestion of the cytological interpretation of the pleural fluid.

The patient underwent a first session of chemotherapy (gemcitabine and carboplatin), uneventfully, by day 19 after admission. However, 12 hours after the chemotherapy infusion the clinical status deteriorated, with dyspnea that didn't improve with treatment, bronchospasm and restlessness. The intensive care unit was contacted and agreed to receive the patient. Despite all the efforts made to stabilize the patient, in a 12 day span the patient didn't show any signs of clinical improvement and died after 31 days of hospital admission.

Case 2.

Patient of 60 years-old, male, with past history of colon adenocarcinoma (Stage IIB), treated with conservative surgery and chemotherapy (5-FU), stable for the last 6 months and under surveillance in Oncology consultation. The imaging exams didn't show any signs of relapse and the analytical work-up remained within normalcy. The tumor markers levels were unwavering and clinically, there was nothing relevant to pin-point.

By month 7, the patient underwent the regular blood work, in which a considerate eosinophilia is noted: 4800/microL (AC). All the causes of eosinophilia were discarded, namely the infectious and allergic ones. The patient was strictly surveilled for 3 months, where was noted a pattern of oscillating levels of eosinophilia, that didn't exceed the 8.300 micro/L (AC). Concurrently, there was a rise in the tumor markers levels and the imagiological control Ct-scan found evidence of neoplastic recurrence. The patient was eligible for chemotherapy (PS 2), started 5-FU without significant side effects. The eosinophilia diminished (1400 micro/L (AC) minimum, 2500 micro/L (AC) maximum) was oscillating during all the treatment.

Due to clinical deterioration (PS 4) the treatment was suspended, admitted in the Surgery Department for comfort and end-life measures. The patient died 2 weeks after treatment discontinuation.

Discussion

Eosinophils were recently considered multifunctional cells, involved in several organ homeostasis, innate/adaptive immunity and eventually involved in oncogenicity. The goal of this article is to focus on the significant prognostic meaning of paraneoplastic eosinophilia and the importance of the level of suspicion. Eosinophilia secondary to tumor growth or involvement is rare to find, has no specific pattern or cut-off and has an unclear onset^[7].

As seen in the cases described above, the analytical irregularity in the eosinophils varies according to the patient's context, namely if there is a previous tumor diagnosis or if the patient is naïve from the neoplastic point of view. When there is no tumor diagnostic but there is a high suspicion of an oncological process (clinical deterioration, suggestive patient history of tumor existence and suspicious imaging), the high eosinophilia count is an important factor to take into consideration. In the cases reported in the literature, the paraneoplastic eosinophilia related to undiagnosed cancer is frequently significant in absolute count (> 10.000 eosinophils, [AC])^[8], with no particular filiation to a specific tumor type. There are reports of paraneoplastic eosinophilia as presentation of tumors with gastrointestinal origin, lung, thyroid and kidney.

For instance, the paraneoplastic eosinophilia associated to lung cancer is usually associated with shortness of breath and wheezing^[9], some of the features also observed in our patient (case 1) at presentation; although the tumor type was not identified, there was a high level of suspicion of lung primary. The eosinophil AC described in the case of a patient with lung adenocarcinoma^[9] ranged from 23.539 to 92.840, decreasing as the oncologic therapy proceeded, but never normalized. In our patient, the eosinophil AC ranged from 4.000 to 19.200, and the descent in the AC wasn't influenced by any therapy.

There are 2 cases^[1,10] of paraneoplastic eosinophilia associated to metastized kidney cancer (both histologically clear cell renal cell carcinoma), in which the AC at presentation varied from 48.000-78.000 to 3.128 eosinophil AC at the time of the case presentation, which states the unfeasibility of considering cut-off levels to suspect the paraneoplastic origin of the eosinophilia.

The same applies to tumors from gastrointestinal tract. In the case we describe, the eosinophil AC was raised but remained in the range of 4800-8300 AC in a 3-month span, oscillating as we performed the work-up needed to discard all the other eosinophilia causes and in the meantime, concurrently with the tumor markers rise, the image exam confirmed the tumor recurrence. In that moment we considered the eosinophilia was, indeed, paraneoplastic in nature. The tumor, localized in the sigmoid, showed also imaging evidence of liver and bone metastasis. There was also a case^[8] of a cecum adenocarcinoma with high eosinophilia at presentation, with liver metastasis when staged.

In all cases, the prognostic was poor.

As far as the investigation of the eosinophilia is concerned, there isn't evidence of the need of bone marrow biopsy for diagnostic purposes, since the paraneoplastic eosinophilia is easily related to an oncologic origin even when it has an unknown origin. The suggestive clinical history of asthenia, weight loss and physical decline added to the analytical findings are usually enough to suspect its neoplastic cause. The identification of the tumor localization is based upon imaging and after staging, a treatment protocol is considered having in account the patient's performance status. In theory, the eosinophilia will normalize with the tumor treatment and eradication.

Conclusion

When faced with eosinophilia of unknown origin, the neoplastic disease must always be taken into account, but the physician must always perform a complete anamnesis and clinical history, that will certainly provide valuable clues to suspect the eosinophilia origin. To date, all the cases reported (including our own) make reference to paraneoplastic eosinophilia frequently observed in disseminated neoplastic disease, inevitably related to poor prognosis.

Conflict of interest

There were no financial disclosures or mentions concerning any author, as well as no conflict of interest.

Consent

By the time this article was written, both patients (case 1 and case 2) were deceased. In case 1, the spouse has given consent for the case to be published, the same for the case 2.

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References

1. Wei-Wei Z, You-Yan G, Xin-Min L. Paraneoplastic Eosinophilia in Clear Renal Cell Carcinoma. *Chin Med J*. 2015,128: 2271-2272
2. Pandit R, Scholnik A, Wulfekuhler L, Dimitrov N. Non-small-cell lung cancer associated with excessive eosinophilia and secretion of interleukin-5 as a paraneoplastic syndrome. *Am J Hematol*. 2007, 82 :234-7
3. Nathan DM, Cherie HD; Micah M, Andrew L; Matthew CF; Steven IP, et al. Diagnostic Complexities of Eosinophilia. *Arch Pathol Lab Med*. 2013, 137:259-269
4. Tefferi A. Blood eosinophilia: a new paradigm in disease classification, diagnosis, and treatment. *Mayo Clin Proc*. 2005, 80:75
5. Roufosse F, Weller PF. Practical approach to the patient with hypereosinophilia. *J Allergy Clin Immunol*. 2010, 126:39
6. Lorraine CP, David EG. Paraneoplastic Syndromes: An Approach to Diagnosis and Treatment. *Mayo Clin Proc*. 2010, 85: 838-854
7. Scarlata, F. Eosinophils and eosinophilia. *Le Infezioni in Medicina*. 2015, 4:307-312
8. George KA, George HS, Panagiotis K, George M, Stavros T, Evaggelos T, et al. Disseminated Colon Cancer With Severe Peripheral Blood Eosinophilia and Elevated Serum Levels of Interleukine-2, Interleukine-3, Interleukine-5, and GM-CSF. *Journal of Surgical Oncology*. 2005, 89:273-275
9. Cheng L, Yee-Min J, Wen-Chiuan T, Ping-Ying C, Woei-Yau K. Rapidly evolving asymptomatic eosinophilia in a patient with lung adenocarcinoma causes cognitive disturbance and respiratory insufficiency: Case report. *Oncol Lett*. 2013, 5(2): 495-498
10. Tilman T, Stefan W, Claus H, Stefan H, Marius H, Joerg H, et al. Severe paraneoplastic hypereosinophilia in metastatic renal cell carcinoma. *BMC Urology*. 2012, 12:7