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Nasal and systemic eosinophilia associated with solid intestinal tumors, a case report and review of the literature.

The authors report the study of a clinical case, which presented eosinophilia both in the secretion of the nasal mucosa and in the blood count. After a careful examination of all the pathologies related to hypereosinophilia, through a clinical study, they have documented the presence of an adenocarcinoma located in the ileocecal junction of the colon. From what has been documented it is clear that only a clinical observation of precision, carried out above all through nasal cytology and colonoscopy, is able to diagnose an important pathology, such as oncology.
For the literature review we used the Scopus and PubMed search engines to analyze other authors who were interested in the relationship between eosinophilia and colorectal cancer. Much of the studies analyzed reported a close relationship between the presence of tissue eosinophilia and tumor, and the prognosis of colorectal cancer.

KEY WORD: Colorectal cancer, Eosinophils, Hypereosinophilia

Introduction

Eosinophils are granulocytes that originate from the bone marrow, endowed with pleiotropic functions in various pathologies and explicating a key role in the late and chronic phases of inflammatory and allergic reactions.
Granulations of eosinophilic granulocytes were first observed in 1846 by Wharton, in preparations of non-stained peripheral blood cells. The term "eosinophilia" was introduced later by Paul Elrich (1879) who described the intense coloration of granules induced by eosin [1].
The involvement of eosinophils in some clinical conditions such as parasitic diseases, allergic diseases and asthma, skin changes and some neoplastic diseases, was highlighted towards the end of the last century [2].
In 1908 Ellis documented hypereosinophilia in asthma [3].
In 1922 Huber and Koessler [4] detected massive infiltration of eosinophils in patients who died of asthma. Until the beginning of the seventies it was believed that eosinophils, intervening in the degradation of mast cell mediators, were decisive in improving allergic processes [5]. In the same period it was definitively ascertained that eosinophils and their products exerted a direct toxic action on parasites [6].
Only towards the end of the eighties was eosinophils recognized the precise role of cell effector and mediator of tissue damage, in asthma and related allergic diseases [7,8].
Moreover, at the conjunctival level the presence of eosinophils can be linked not only to allergic forms, but

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TABLE I - *Causes of allergy associated eosinophilia mod* [11]

Mild degree of eosinophilia
– Allergic riniti
– Asthma
– Atopic dermatitis
– Eosinophilic esophagitis
– Drug allergy

To severe degree of eosinophilia
– Chronic sinusitis (especially polypoid and aspirin-exacerbated respiratory disease)
– Allergic bronchopulmonary aspergillosis
– Chronic eosinophilic pneumonia
– Drug allergy (drug rash with eosinophilia and systemic symptoms [DRESS] syndrome)

TABLE II - *Commonly implicated pharmaceuticals in drug rash with eosinophilia and systemic symptoms (DRESS) syndrome mod* [11]

– Antibiotics: Penicillins, cephalosporins, dapsone, sulfa-based antibiotics
– Xanthine oxidase inhibitor: Allopurinol
– Antiepileptics: Carbamazepine, phenytoin, lamotrigine, valproic acid
– Antiretrovirals: Nevirapine, efavirenz
– Nonsteroidal antiinflammatory drugs: Ibuprofen

TABLE III - *Select parasit infections*

Helminthic infections

Nematodes
– Angiostrongyliasis costaricensis
– Ascariasis
– Hookworm infection
– Strongyloidiasis
– Trichinellosis
– Visceral larva migrans
– Gnathostomiasis
– Cysticercosis
– Echinococcosis

Filariases
– Tropical pulmonary eosinophilia
– Loiasis
– Onchocerciasis

Flukes
– Schistosomiasis
– Fascioliasis
– Clonorchiasis
– Paragonimiasisasciolopsiasis

Protozoan infections
– Isospora belli
– Dientamoeba fragilis
– Sarcocystis

TABLE IV - *Eosinophilia associated with connective tissue, rheumatologic, and autoimmune disease. Mod* **[11]**

– *Eosinophilic fasciitis that cause eosinophilia mod* [111]
– Eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis)
– Dermatomyositis
– Severe rheumatoid arthritis
– Progressive systemic sclerosis
– Sjögren syndrome
– Thromboangiitis obliterans with eosinophilia of the temporal arteries
– Granulomatosis with polyangiitis (Wegener syndrome)
– Systemic lupus erythematosus
– Behçet syndrome
– IgG4-related disease
– Inflammatory bowel disease
– Sarcoidosis
– Bullous pemphigoid
– Dermatitis herpetiformis (celiac disease)

TABLE V - *Primary eosinophilias. mod* [11]

– Idiopathic hypereosinophilic syndrome : sustained peripheral eosinophilia at greater than 1500 cells/μL with associated end-organ damage.

– Lymphoproliferative hypereosinophilic syndrome: sustained peripheral eosinophilia at greater than 1500 cell/μL, often associated with rash, aberrant T-cell immunophenotypic profile, often steroid responsive.

– Myeloproliferative hypereosinophilic syndrome : sustained peripheral eosinophilia at greater than 1500 cell/μL, often features of splenomegaly, heart related complications, and thrombosis. Can have associated FIP1L1-PDGFRA and other mutations and are often steroid resistant. Patients can be considered to have a diagnosis of chronic eosinophilic leukemia.

– Episodic eosinophilia associated with angioedema (G syndrome): cyclical fevers, swelling, hives, pruritus, marked eosinophilia, and IgM elevation. Aberrant T-cell phenotypes often associated.

TABLE VI - *Malignancy-associated eosinophilia. Mod* [11]

Blood-related neoplasms

– Acute or chronic eosinophilic leukemia
– Lymphoma (T cell and Hodgkin)
– Chronic myelomonocytic leukemia

Solid organ–associated neoplasms
– Adenocarcinomas of the gastrointestinal tract (gastric, colorectal)
– Lung cancer
– Squamous epithelium related cancers (cervix, vagina, penis, skin, nasopharynx, bladder)
– Thyroid cance

TABLE VII - *Entities that can be associated with eosinophilia*. Mod [11]

– Rejection of a transplanted solid organ
– Graft-versus-host disease after hematopoietic stem cell transplantation
– Kimura disease and epithelioid hemangioma
– Eosinophilia-myalgia syndrome/toxic oil syndrome
– Adrenal insufficiency
– Irritation of serosal surfaces
– Cholesterol embolus

also to the presence of other forms of infections, such as Candida albicans, Staphylococcus epidermidis, Chlamydia trachomatis and Staphylococcus aureus [9]. At the nasal and respiratory tract, some studies have documented the presence of eosinophils in the presence of chlamydial infections [10].
However, their increase, based on recent studies, is an indirect index of different conditions. Tab. I-VII) [11]. In addition, the presence of nasal eosinophils in the absence of documented allergies, recently, was framed in a new nosological entity, the NARES [12] if there is only eosinophils or NARESMA if there are eosinophils and mast cells [13].

Case Report

A 45-year-old male subject with recurrent rhinitis emerged in the last quarter. The family history of negative for allergic and / or autoimmune diseases. After completing privacy and informed forms, all patients underwent a physical examination that included rhino-fiberscope with a rhino-fiberscope (Xion Amplaid, Milan, Italy) 4 mm in diameter using disposable sheaths for protection, which objectively documented a pink nasal mucosa with hypertrophic and pale nasal turbinate. Nasal septum basically in axis. Normally the remaining districts observed. During the diagnostic procedure, a cytological nasal fetch was performed. The cytological was carried out crawling 2-3 times a respond (Nasal-scraping®) on the mucosal surface of the central zone the inferior turbinate. The nasal mucosal cells were placed on an electrostatically charged cytology slide (Super Frost Plus Menzel - Gläser, Thermo Scientific, Milan, Italy). The cells were then stained according to the panoptic Pappenheim method (3 min in pure May-Grunwald dye [Carlo Erba, Milan, Italy], 6 min in 50% May-Grunwalddye, 1 min in bidistilled water [Carlo Erba, Milan, Italy] and 30 min in Giemsa solution [Carlo Erba, Milan, Italy] diluted 1:10 v / v). Images with 24 x 50 mm and observed, on fifty observational fields, under an optical microscope (Nikon Eclipse 50i at 100 x enlargement in oil-immersion, the images were acquired using software D - Elements of the Nikon.
The cytological study showed the presence of numerous

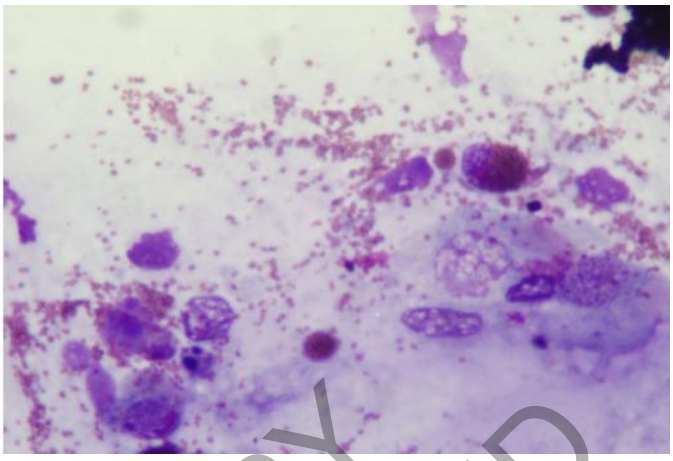

Fig. 1: Eosinophils and eosinophilic granulation. 1000 x magnification in oil immersion.

eosinophils according to the semiquantitative evaluation [14] and with a percentage evaluation of 5%. Some of them were plurilobulated, others in granulation (Fig. 1).
Following this diagnosis, a blood count and an allergy examination were carried out.
The first to evaluate the presence of blood elements that could indicate the possible increase of systemic eosinophils, the second to confirm or exclude the presence of allergy and other immune pathologies responsible for the increase of eosinophils.
These investigations have documented:
– the hemocytometer frame, the presence of eosinophilia greater than 10 x 109 / l, with a percentage equal to 7.5% (300 eos / mm3 8000 leucocytes / mm3);
– Allergic assessment has excluded all forms of allergies, conditions and other infectious and parasitic diseases responsible for hypereosinophilia. Further investigations have excluded lymphoproliferative disorders.
An alteration of the alveus was observed from the anamnestic examination, accompanied by blurred changes located in the right iliac fossa. For this reason, the patient underwent a search for occult blood in the stool, a positive result. Subsequently he was subjected to colonoscopy who documented the presence of a geoformation located in the ileocecal junction.
Histological examination on endoscopic biopsy, then documented an adenocarcinoma. For this reason he was subjected to right hemicolectomy. The histological examination showed a medium-level differentiation adenocarcinoma, infiltrating the wall up to the muscular tunic, with tissue infiltration from eosinophils.

Discussion

Hypereosinophilia in oncological disease was first described in 1893 by Reinbach [15] and is a paraneoplastic phenomenon. Several studies have shown that eosinophils are attracted to tumors by chemotactic factors

[16-18] such as eotaxines and molecular models associated with damage, particularly HMGB1 which is released by necrotic tumor cells [19]. In the context of neoplastic pathology, hypereosinophilia is a reactive phenomenon to the release of eosinophilic cytokines released by non-myeloid cells in an unregulated manner. Approximately 15% of patients with Hodgkin's lymphoma [20] and about 5% of patients with non-Hodgkin's lymphoma have mild peripheral eosinophilia

In Sézary syndrome, due to a T lymphoma with erythroderma manifestation, hypereosinophilia and increased IgE production are due to the production of high levels of Th2 cytokines (IL-5, IL-4). Also some solid tumors can be associated with paraneoplastic eosinophilia; these include transitional cell carcinoma of the bladder, large cell lung cancer and thyroid carcinoma [23], adenocarcinoma of the uterus, stomach and colon [11]. However, the role of tissue-associated eosinophilia associated with the tumor is not clear [16].

In the observed case, a rhinitic picture, apparently connected to an immunoallergic and / or infectious disease, was documented, in the first instance, at the visit and the ENT investigations. However, subsequent investigations, allergologic and hematological, have not detected these conditions and have also excluded lymphoproliferative diseases. Only a thorough medical history and team work allowed to highlight the relationship between nasal, hematological eosinophilia and colon tumors, in a clinical case that could be diagnosed as a form of NARES.

Our literature review of the Scopus and PubMed databases used key words "Eosinophilia and Tumors" and "Eosinophilia and Colorectal Cancer". The articles examined showed that eosinophilia can be considered a prognostic factor in colorectal cancer, its presence positively influences the metastatic evolution of carcinoma.

Conclusions

When we are faced with unclear conditions it is always good to go over the diagnostic-therapeutic algorithm, especially in the team. In the case discussed, moreover, two specific investigations made it possible to perform a precision diagnosis: Nasal Cytology laid the groundwork for the suspicion of a paraneoplastic component of the disease, and the colonoscopy that allowed to evaluate this condition and diagnose an important pathology like the oncological one. The literature confirmed the role of eosinophilia as a marker of numerous cancers and is a valuable program in the surveillance of colorectal cancer.

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