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OLGU SUNUMU CASE REPORT

A case of sustained eosinophilia and adenocarcinoma of the prostate: natural defense or coincidence?

Uzun süreli eozinofili ve prostat adenokarsinomu olgusu: Doğal savunma mekanizması mı, yoksa sadece birliktelik mi?

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ABSTRACT

Eosinophils are usually considered as an end-stage cell, involved only in host protection against parasites or allergic diseases. However, there is accumulating evidence showing that eosinophils are multifunctional leukocytes involved in several immunological responses. In this report, a patient with persistent eosinophilia, who was finally diagnosed as prostatic adenocarcinoma, is presented and discussed. While any tumor can induce eosinophilia, prostate carcinoma-related eosinophilia is quite rare, according to the current medical literature. Moreover, some remarkable findings about eosinophils and prostate tumor cells, other than the recently reported ordinary "eosinophil-tumor cell" interactions, are also highlighted.

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Key words: Prostate cancer, prostatitis, prostate specific antigen, eosinophil, eosinophilia, cadherin

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ÖZET

Eozinofiller, genellikle sadece organizmayı parazit infeksiyonlarından koruyan ya da allerjik hastalıklardan sorumlu hücreler olarak değerlendirilir. Ancak eozinofillerin değişik immün yanıtlarda yer alan çok fonksiyonlu lökositler olduğunun birçok kanıtı vardır. Bu yazıda, uzun süreli eozinofil yüksekliği olan ve sonuçta prostat adenokarsinomu tanısı alan bir hasta sunulmakta ve tartışılmaktadır. Herhangi bir tümör eozinofiliye neden olabilirse de, mevcut tıp literatürüne göre prostat karsinomu ilişkili eozinofili olgusu oldukça nadirdir. Ayrıca, bilinen eozinofil-tümör ilişkisinin ötesinde, eozinofiller ve prostat tümör hücreleri arasında yakın zamanlarda bildirilmiş olan ve dikkate değer bazı etkileşimler de bu olguda ele alınmaktadır.

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Anahtar kelimeler: Prostat kanseri, prostatitis, prostat spesifik antijen, eozinofil, eozinofili, katedrin

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INTRODUCTION

Eosinophils are bone marrow-derived granulocytes that are normally found in small numbers in either the peripheral blood or the tissues. They represent 1% to 5% of the leukocytes with an upper limit of 0.4 x 10^9/L. Some laboratories list higher upper values, in particular in children (as high as 0.75 x 10^9/L). Eosinophils are usually considered an end-stage cell, involved only in host protection against parasites or allergic diseases. However, there is accumulating evidence showing that eosinophils are pleiotropic multifunctional leukocytes involved in initiation and propagation of diverse inflammatory responses, as well as modulators of innate and adaptive immunity[1,2].

Causes of eosinophilia are divided into three main categories: reactive eosinophilia, which is a response to a primary (usually non-hematological) disease; clonal eosinophilia, which can be described as eosinophils that are part of a neoplastic clone; and idiopathic eosinophilia, which does not fall into either of the first two categories. In reactive eosinophilia, the underlying disorder is most commonly helminthic infection or atopic disease. Other causes include malignancy, vasculitis, an allergic response to drugs, and several other disorders that are less commonly the cause of eosinophilia[3].

In addition to hematologic neoplasms with eosinophilia (clonal expansion), solid tumor-associated eosinophilias can also be seen. Blood and tissue eosinophilia may be observed in patients with tumors of epithelial cell origin. Examples are tumors of the thyroid gland, stomach, liver, and bladder. The role of eosinophils under these conditions remains unclear[2].

In this paper, a patient with persistent eosinophilia, who was finally diagnosed as prostatic adenocarcinoma, is presented and discussed. While any tumor can induce eosinophilia, prostate carcinoma-related eosinophilia is quite rare, according to the current medical literature. Moreover, some remarkable findings about eosinophils and prostate tumor cells, other than the recently reported ordinary "eosinophil-tumor cell" interactions, are also highlighted.

CASE REPORT

A 58-year-old man was referred to the allergy clinic with elevated peripheral blood eosinophil count, which was detected in his annual medical check-up. In addition to eosinophilia, another abnormal finding was moderately elevated prostate specific antigen (PSA) (5.7 ng/mL), although he had no symptom indicative of a prostate pathology, such as nocturia, hematuria, dysuria, frequency, or incontinence.

Because of these (probably) unrelated pathological findings, a two-way investigation was initiated by the allergy and urology clinics.

Allergic Investigation

He had been diagnosed as seasonal allergic rhinitis due to pollen allergy about five years apo, and was receiving pre-seasonal allergen immunotherapy annually from late winter to early spring. He was under treatment with valsartan *(angiotensin II receptor antagonist)* and atenolol *(β1 receptor specific antagonist)* for arterial hypertension. No other medication, supplement or herbal product was noted.

Laboratory tests did not show any abnormality other than eosinophilia: whole blood count revealed 13% eosinophils (1560/mm^3) with 12.000/mm^3 white blood cells. Other cell lines and hemoglobin were in normal ranges. The increased number of eosinophils (with normal morphology) was confirmed on peripheral blood smear. Erythrocyte sedimentation rate (ESR) was 7 mm per hour. Repeated stool examinations and serology for parasites were negative. Blood chemistry values, including glucose, blood urea nitrogen (BUN), creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein, and albumin, were in normal ranges. Auto-antibodies including perinuclear/circulating anti-neutrophil cytoplasmic antibodies (pANCA, cANCA), antinuclear antibodies (ANA), and anti-double-stranded (ds)DNA

were negative. Chest X-ray and upper abdominal ultrasonography were normal. In summary, except for pollen allergy, no definitive cause for eosinophilia was identified. However, eosinophilia was not explained by the pollen allergy since atmospheric pollen concentration was very low during the investigation period. Thus, there was no antigenic stimulus to augment allergic inflammation, in other words, to increase the eosinophil counts.

Urological Investigation

Urological investigation executed by an urologist revealed a presumptive finding to elucidate the high PSA level: on transrectal prostate ultrasonography, even though the gland was of normal size and had nearly homogeneous echo texture, a small (9 x 8 x 9 mm) hypoechoic area at the right transitional zone was distinguished. This finding was primarily concluded as prostatitis and a 10 day course of doxycycline was given. At the end of the trial, because PSA level remained high, a prostate biopsy was suggested.

Biopsy exposed the prostate adenocarcinoma as a single focus with the largest cross-sectional dimension of 2.5 x 0.9 cm. The surrounding tissue was tumor-free and the prostate capsule intact. In other words, the tumor was confined to the prostate.

Outcome

After treatment with transurethral prostate resection, PSA level reduced to normal ranges, as expected. In addition, the number of the peripheral eosinophils also decreased. On repeated counts on different days, the eosinophil count remained within 100 to 150 cells per cubic milliliter and never increased again.

The history of the case and diagnostic steps are summarized as a flow diagram in Figure 1.

DISCUSSION

In the presented case, we report a challenging clinical observation: our patient presented two unrelated laboratory abnormalities without clinical signs that were not indicative for each other, but treatment of one brought about amelioration of the other. In such cases, a physician usually considers the event to be a coincidence. This opinion is generally true, but not always, as seen in our case.

Furbert-Harris and colleagues described the inhibitory activity of eosinophils against DU 145 and PC-3 prostate tumor cells growth in vitro[4]. In their study, cultures of DU 145 and PC-3 cells were incubated with peripheral blood eosinophils from allergic or asthmatic individuals and also with eosinophil-cultured supernatants. Results clearly demonstrated that activated eosinophils (eosinophils from the peripheral blood of allergic and asthmatic individuals) inhibited the growth of prostate tumor cell lines in vitro. Non-allergic eosinophils were less effective than allergic eosinophils as was expected, since they were non-activated and therefore contained far fewer granules, and hence less toxicity.

The same investigators, based on the roles of cell adhesion molecules (CAMs) in cancer metastasis, studied the ability of activated eosinophils to modulate the expression of intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, endothelial leukocyte adhesion molecule (ELAM)-1, E-cadherin, and N-cadherin expression on human prostate cancer cell lines. They found a modulatory activity of activated eosinophils on CAM expression. Most significantly, the metastasis suppressor molecule, E-cadherin, was enhanced on prostate cancer cells by activated eosinophils and cytokines [interleukin (IL)-10 and IL-12], which are produced by activated eosinophils[5]. This finding may suggest that eosinophils help to confine tumor cells within the prostate.

Ishiguro et al., reported an 80-year-old male with prostatic carcinoma who developed eosinophilic pneumonia and intrathoracic metastases[6]. Initial presentation complaints included shortness of breath, cough and fever. Pelvic computed tomography scan revealed a massively enlarged prostate. The histopathological diagnosis was prostatic adenocarcinoma. After treatment of the prostatic carcinoma, all initial

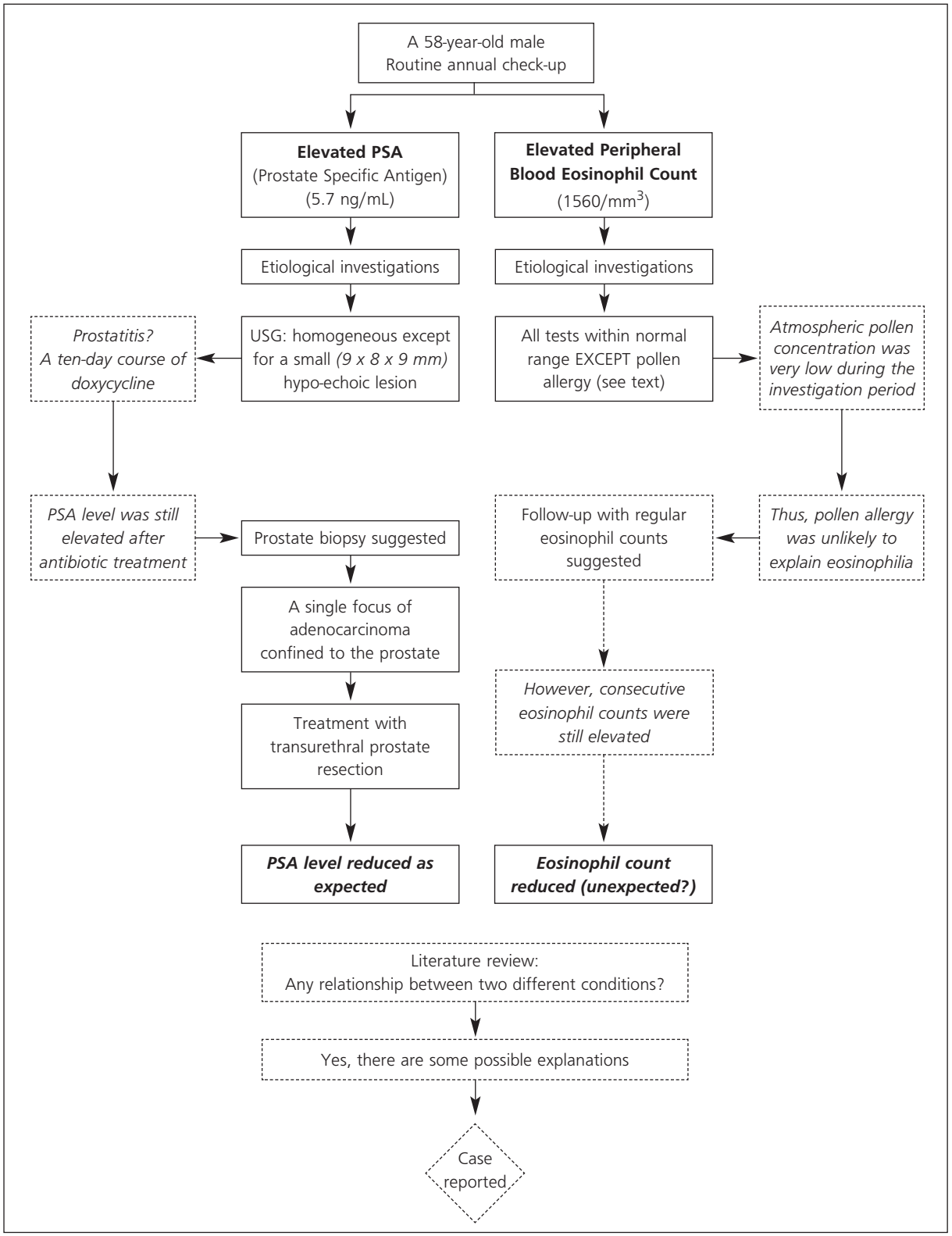

Figure 1. Summary of the case.

pulmonary manifestations, including eosinophilic pneumonia, disappeared.

In light of the presented case and relevant facts in the literature, a prospective study in patients with prostate carcinoma, or in patients with sustained eosinophilia, may support some hypotheses including:

1. Prostate carcinoma may be the only cause of sustained eosinophilia,

2. Serial eosinophil counts may be useful in the follow-up of patients with prostate cancer,

3. Uncertain prostate lesions and/or elevated PSA levels in a patient with atopy should be investigated in detail since neoplastic tissues can grow in an unusual pattern or mimic prostatitis through the agency of activated eosinophils.

In conclusion, when dealing with a patient with eosinophilia, the actual presence of eosinophilia needs to be confirmed with repeated counts. If the eosinophil counts remain elevated, a focused history and detailed investigation oriented to both usual and unusual causes should be performed.

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