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Participation and the possible role of eosinophils in the inflammatory process in chronic forms of pulmonary tuberculosis

Keywords: *eosinophils, chronic pulmonary tuberculosis, histology.*

Introduction

In patients with pulmonary tuberculosis in the blood and lung tissue a significant number of eosinophils is often revealed, but the role of which is not always straightforward and clear in the pathogenesis of the disease. This blood eosinophilic reaction in pulmonary tuberculosis may reflect or not reflect the intensity of their presence in the lungs and varies widely. Most often, eosinophilia in patients with pulmonary tuberculosis associated with the ongoing anti-TB chemotherapy and initial allergic state of an organism [1, 10 – 13].

But the cases of eosinophilic reaction of blood are often recorded before to appointment of anti-tuberculosis therapy in patients with pulmonary tuberculosis. Mikheeva KO et al. (2013) in its study established that initially mild eosinophilia was recorded in every fifth patient with tuberculosis, while the maximum eosinophilia was observed in patients with disseminated form with accompanied hyperactivity of these cells [7, 9].

Eosinophils are multifunctional leukocytes involved in the pathogenesis of allergic diseases, parasitic infestations, bacterial and viral infections, tissue damage, and anti-tumor immunity, and affect the sexual cycle in females, pregnancy [6, 14]. In evolution eosinophils occurred in higher vertebrates to destroy foreign antigens (primarily helminth) to restrict of generalization of immune response to local reaction at the site of penetration of the antigen.

As a result of the cascade of immunological reactions resulting in the presence of worms, after binding of eosinophils to Fc-fragments of IgE and IgG on the parasite surface the degranulation of cells occurs, followed by the extracellular cytolysis of multicellular parasite. This hypereosinophilia observed in the larval migration, is the basis for antiparasitic protection.

Eosinophil's products may also block the activity of mast cells, allowing their recovery, limiting the development of hyperallergic reactions by isolating inactivating enzymes, neutralizing histamine, slow reacting substance of anaphylaxis, lytic platelet factor, heparin, et al., as well as «devouring» granules secreted by mast cells. In addition, substances secreted by eosinophils can inhibit the proliferation of T-lymphocytes and are capable to regulate cell-mediated immunological responses [16]. The spectrum of cytokines produced by eosinophils, similar to that of basophils and mast cells, and includes typical Th2-cytokines. That is, eosinophil are possess physiological dualism and capable of playing both pro-allergic and protective anti-allergic role during various pathological processes.

Most often eosinophils are seen as markers of allergic conditions, taking part in all phases (early, delayed, and late) of allergic inflammation [14]. Indeed, the eosinophilic inflammation in the lung tissue is revealed in «allergic» diseases (eosinophilic pneumonia, bronchial asthma, allergic bronchopulmonary aspergillosis, parasitic lung disease, syndrome Charg-Strauss, allergic reactions caused by medication, drugs, etc.). But tissue eosinophilia is observed in diseases in which the pathogenesis of allergic reactions do not play a significant role (Langerhans-cell histiocytosis, lymphomas, Hodgkin's disease, respiratory infections caused by cytomegalovirus, retroviruses, etc.) [1, 17]. When tumor processes occurring with eosinophilia, it was detected the ability of eosinophils to damage of host tissue and stimulate the processes of fibrosis [5].

When disseminated destructive forms of tuberculosis with multiple resistance with background eosinophilia there is registered an increase in blood regulatory T cells (CD4 + CD25 + Foxp3 +) with immunosuppressive activity which manifests hyperproduction of TGFβ and IL-10 and decreased production of IL-2 [15] – it is possible explain, in particular by immunosuppressive activity of mycobacteria.

It was established that eosinophilia in pulmonary tuberculosis combined with an increase in the absolute content of B lymphocytes (CD20 +) and the concentration of IL-5 under IFN-y deficiency in the blood that may indicate the ability of eosinophils to displacement the Th1 / Th2 balance toward Th2-associated reactions – that often contributes to the progression of the pathological process [9]. The authors conclude that the mechanism of formation of eosinophilic blood reaction in tuberculosis is mediated by genetically determined hypersecretion of key eosinophil-activating mediators (IL-5 and eotaxin) by blood cells and overexpression of IL-5RA on the membrane of eosinophilic granulocytes, – which in turn contributes to prolonged stay of eosinophilic leukocytes in blood circulation during tuberculosis infection.

Thus, eosinophilic granulocytes, producing the key mediators of cellular and humoral immune response, able to contribute a some part to the common cytokine imbalances, forming in TB infection, and maintain the destructive changes in the lung tissue.

Eosinophils are not a mandatory component of granulomas and other structural formations of the lung tissue in pulmonary tuberculosis. But it is possible that the cytotoxic (microbicidal) potential of eosinophils can be sent to the *Mycobacterium tuberculosis*, causing their positive contribution to the inflammatory process.

In general, to date, there is no consensus on the desirability and value of eosinophilic reaction in the blood of tuberculosis infection [12]. It remains relevant fundamental question about the role of eosinophilic granulocytes in pulmonary tuberculosis: do they protect the macro-organism from Mycobacterium tuberculosis or, on the contrary, serve as an additional factor favoring their persistence?

The aim of this study was to investigate the number of eosinophils and their distribution in the different structures of the lung tissue with fibrous-cavernous lung tuberculosis and tuberculoma with varying degrees of specific inflammatory activity to ascertain their participation in the specific inflammatory response.

Materials and methods

Lung tissue was examined from 45 patients with diagnosis of fibro-cavernous tuberculosis (FCT) and 46 patients with tuberculoma that surgical intervention due to the inefficiency of prior chemotherapy or long-term progression of a specific inflammatory process. Of the 46 patients with tuberculomas in most cases it was determined tuberculoma-caseoma – 39 patients, of which 10 cases were multiple and 7 - were conglomerate type. Tuberculomas of infiltrative-pneumonic type were detected only in 4 observations and in 3 cases there were tuberculomas with initial cavern formation. All last 7 cases observed on the background of a high degree of specific inflammatory activity by morphological signs.

Eosinophils were detected in lung tissue in conventional manner staining of histological specimens with hematoxylin and eosin. We studied the wall cavity or capsule tuberculoma and neighboring lung tissue, which contain typical tuberculous lesions structural formations and restructuring. Histological specimens were analyzed using microscopes Olympus CX21 and/or Olympus BX51.

Based on morphology determination of the degree of activity of tuberculous inflammation in the lung tissue (referring to the thickness of the layers wall cavity or tuberculoma, their cell composition, specific structures of the perifocal areas, severity of fibrous strands, etc.) [2, 3], all biomaterial was divided into 4 groups. The group number 1 included 25 cases with FCT and morphologically determined a high activity of specific inflammatory process, the group number 2 consisted of 20 cases with moderately-low FCT activity; group 3 – 25 cases with tuberculoma and a high degree of activity of specific inflammatory process, and group 4 – 21 cases with tuberculoma and a low degree of inflammatory activity.

Semiquantitative evaluation of the presence and location of eosinophils in the lung structures was carried out according to the conventionally accepted working gradation: «small» – consistent with the presence of <15 eosinophils in one field of view of microscope, «many» – ≥15 eosinophils in one field of view of microscope, with an operating microscope magnification x400.

Statistical analysis of the material was carried out with the help of licensed software included in Microsoft Office Professional 2000 License Russian Academic OPEN NO LEVEL № 17016297 package Athlon IBM PC in Excel according to the recommendations Lapach S.N. et al. (2001) [8]. All results are presented as: n - number of examinees in the group, in the proportions and percentages indicating the confidence interval (CI). If the analyzed values were ≤ 5, was used Fisher's exact test [4]. Calculations criterion values and confidence intervals were carried out at a given significance level ≤ 0.05.

Results and discussion

It is found that for high specific activity of inflammation in patients with FCT (group 1) eosinophils were identified in various pulmonary structures in all 25 cases (100,0 % of patients), whereas in the group with low activity FCT (group 2) eosinophils are found only in 9 patients (45.0 %), p <0.001 (CI 33,2-76,8). To our opinion it's indicating about a direct connection of eosinophils with the degree activity of inflammation.

Thus, in patients with morphologically highly activity at FCT eosinophils primarily determined in granulating layer of the cavity wall and at the border with necrosis, 64.0 % of the cases (mainly in small amounts), in 44.0 % of patients – in fibrous layer of the cavity (in larger quantities). In 80.0 % of cases, the presence of eosinophils was

found in a number of specific histological structures – in focuses of dropout near cavity (small foci, the foci of medium size, large foci of lipoid pneumonia – as a manifestation of an early stage of caseous pneumonia), in granulomas and foci of specific pneumonia (gradation – many).

At little activity of specific inflammation in FCT cases (group 2), eosinophils in foci of specific pneumonia were absent, and totally in the above mentioned structures eosinophils were detected only in 15.0 % of patients (Table. 1). Thus, the presence of eosinophils in the cavity structures and specific inflammation foci (including dropout lesions, granulomas, specific foci of pneumonia) has been associated with high activity of tuberculous process. Since these areas are characterized by most active morpho-functional lung tissue restructuring during exacerbation of chronic tuberculous inflammation, it is possible to assume an active antimycobacterial eosinophils participation in the implementation of inflammatory reactions.

In small amounts (and without significant differences between 1 and 1 patient groups with FCT) eosinophils were found in the walls of the bronchi, near the bronchi and blood vessels, inside the alveoli and alveolar septa as well as in lymphoid cell clusters (see Table. 1).

In lung tissue specimens of patients with the FCT and the low activity of tuberculosis process significantly more eosinophils determined in inflammatory cell clusters and foci of nonspecific pneumonia (20.0 % versus 0.0 % in group 1, p = 0.033) (see Table. 1), – that it can be used as a concomitant feature of low activity of inflammatory process at FCT.

For chronic undulant course of pulmonary tuberculosis in the form of FCT it is characteristic the development of pulmonary fibrosis, in particular in the form of so-called connective tissue scarring resulting from healing of pre-existing small foci of inflammation. It was found that in fields of fibrosis and fibrotic strands there is tendency (p = 0.066) to more quantity of eosinophils in patients with low activity of FCT (35.0 % respectively in the cases in group 2 against 12.0 % in group 1), – that would reflect the positive trends in the cellular composition at the «healing» of inflammation in low

Table 1

The incidence of eosinophils in various lung structures in patients with fibro-cavernous tuberculosis of lung depending on the activity of specific inflammation (n = 45) (number of cases in group, %)

The studying lung structure	1 group (n = 25)						2 group (n = 20)						p (CI)
	The number of eosinophils in the field of view												
	Few		Many		Total		Few		Many		Total		
	n	%	n	%	n	%	n	%	n	%	n	%	
Granulation layer of the wall of the cavity + border with necrosis	15	60,0	1	4,0	16	64,0	0	0,0	0	0,0	0	0,0	p < 0,001 (45,2–82,8)
Fibrous layer of the cavity wall	7	28,0	4	16,0	11	44,0	0	0,0	0	0,0	0	0,0	p < 0,001 (24,5–63,5)
Caseous-fibrosis nodules near to the cavern + granulomas + lesions of specific pneumonia	14	56,0	9	24,0	20	80,0	2	10,0	1	5,0	3	15,0	p < 0,001 (42,8–87,2)
Fields fibrosis + fibrous strands	2	8,0	1	4,0	3	12,0	3	15,0	4	20,0	7	35,0	p = 0,066 (47,5–1,5)
The wall of the bronchi, peribronchial area	3	12,0	0	0,0	3	12,0	3	15,0	0	0,0	3	5,0	p > 0,05
Near vessels	0	0,0	0	0,0	0	0,0	1	5,0	0	0,0	1	5,0	p > 0,05
Inside the alveoli and alveolar septa	1	4,0	1	4,0	2	8,0	2	10,0	0	0,0	2	10,0	p > 0,05
Lymphoid cell clusters	0	0,0	1	4,0	1	4,0	1	5,0	0	0,0	1	5,0	p > 0,05
Focuses of nonspecific pneumonia + inflammatory cell accumulation	0	0,0	0	0,0	0	0,0	3	15,0	1	5,0	4	20,0	pF = 0,033 (37,5–2,5)

Notes: p – the level of significance of differences of frequency of eosinophils occurrence in the lungs specimens of patients from 1 and 2 groups as a whole («Total»), pF – the level of significance of differences of frequency of eosinophils occurrence in the lungs specimens of patients from 1 and 2 groups as a whole («Total») with using exact Fisher's test, CI – confidence interval, comparable indicators covering options 1 and 2 groups as a whole («Total») with the reliability of p <0.05.

activity of tuberculosis process in the cases of lung FCT. Probably eosinophils take an active party in this process, as, on the one hand, the specific collagenase of eosinophils can inhibit the excessive formation of collagen in lung tissue, and on the other – on the contrary, eosinophils can stimulate this process [16].

Thus, when a high degree of activity of FCT, eosinophils were observed in specimens of lungs of all patients, with their predominant localization in the wall of the cavity and foci of dropout. At a low degree of FCT activity eosinophils were present in the lung tissue structures and the cavity is less than half of the cases (9 patients, 45.0 %). By reducing the activity of FTC eosinophils have tendency (P = 0.066) detect mainly in fibrotic lung formations (fields fibrosis, fibrotic strands).

When morphologically high degree activity of specific inflammation in patients with tuberculomas (group 3), as with FCT, eosinophils were found in various lung structures in all 25 cases (100.0 % of patients), whereas in the group with low activity eosinophils were found in the lung structures only in 7 patients (33.3 %), p <0.001 (CI 86,8-46,5) – which is also indicative about a direct connection of eosinophil with the activity of inflammation in a particular form of pulmonary tuberculosis as a tuberculoma.

Patients with pulmonary tuberculoma and morphologically high degree of activity of tuberculous inflammation (group 3) have histological changes similar to those in the wall of the cavern: eosinophils determined in almost all patients in the granulation layer of tuberculoma capsule (usually in small amounts, totally, with a separate count of eosinophils at the border necrosis, – at 108.0 % of cases), – while the low activity of inflammation (group 4) – only in one third of patients (Table 2).

This may be indirect evidence in favor of the antimycobacterial activity of eosinophils. In the fibrous layer of tuberculomas capsules with different activity of inflammation detection rate of eosinophils was the same as the active FCT (respectively 64.0 % and in 57.1 % of patients of groups 3 and 4, p> 0.05, and at 44.0 % patients of group 1, p> 0.05) – which could be associated with a more active metabolic processes in this area than in the fibrous layer of the wall cavities at the FCT-cases with small activity of specific process (in 0.0 % of patients, p <0.001, CI 36,0-78,3). That is, if the FCT of the lungs presence of eosinophils in fibrous layer of cavern directly dependent on the activity of the process, when tuberculomas eosinophils present in the fibrous layer of capsules, regardless of the

Table 2

The incidence of eosinophils in various structures of lung tissue in patients with pulmonary tuberculoma depending on the specific activity of inflammation (n = 46) (number of patients in group, %)

The studying lung structure	3 group (n = 25)						4 group (n = 21)						p (CI)
	The number of eosinophils in the field of view												
	Few		Many		Total		Few		Many		Total		
	n	%	n	%	n	%	n	%	n	%	n	%	
Granulation layer of the tuberculoma capsule + border with necrosis	19	76,0	8	32,0	27	108,0	7	33,0	0	0,0	7	33,3	p < 0,001 (86,8–46,5)
Fibrous layer of the tuberculoma capsule	11	44,0	5	20,0	16	64,0	12	57,1	0	0,0	12	57,1	p > 0,05
Caseous-fibrosis nodules near to the tubercyuloma + granulomas + lesions of specific pneumonia	13	52,0	3	12,0	16	64,0	2	9,5	2	9,5	4	19,0	p < 0,001 (19,7–70,2)
Fibrous strands	0	0,0	1	4,0	1	4,0	2	9,5	0	0,0	2	9,5	p > 0,05
The wall of the bronchi	0	0,0	1	4,0	1	4,0	0	0,0	0	0,0	0	0,0	p > 0,05
Near vessels	0	0,0	0	0,0	0	0,0	0	0,0	0	0,0	0	0,0	p > 0,05
Inside the alveoli and alveolar septa	0	0,0	2	0,0	2	8,0	0	0,0	0	0,0	0	0,0	p > 0,05
Lymphoid cell clusters	0	0,0	0	0,0	0	0,0	1	4,8	0	0,0	1	4,8	p > 0,05
Focuses of nonspecific pneumonia + inflammatory cell accumulation	3	12,0	0	0,0	3	12,0	4	19,0	0	0,0	4	19,0	p > 0,05

Notes: p – the level of significance of differences of frequency of eosinophils occurrence in the lungs specimens of patients from 3 and 4 groups as a whole («Total»), CI – confidence interval, comparable indicators covering options 1 and 2 groups as a whole («Total») with the reliability of p <0.05.

degree of inflammatory activity, which is indirectly indicate about activity of these cells, even against weakly represented specific inflammation. The presence of eosinophils in the fibrous layer of tuberculoma could contribute, in particular, to intensive formation of collagen in the structure with the purpose of separating a specific process with long-term persistence of the pathogen.

Like the histological picture at the FCT, in patients with tuberculoma and high degree of inflammatory activity the eosinophils were also determined in 64.0 % of cases in the foci of dropout near tuberculoma, in granulomas and foci of specific pneumonia, – whereas at low activity of specific inflammation – only in 19.0 % of patients, p <0.05 (see Table 2).

Thus, the presence of eosinophils in the structures of tuberculoma and foci of specific inflammation (including dropout lesions, granulomas, specific pneumonia lesions) was also directly related to the high activity of tuberculous process.

In all the other structures of the lung at tuberculomas (in the walls of the bronchi, near the bronchi and blood vessels, inside the alveoli and alveolar septa, in lymphoid cell clusters) eosinophils, as with FCT, detected rarely, regardless of the activity of tuberculous inflammation (see Table 2).

In contrast to the FCT, when pulmonary tuberculomas with different activity of tuberculosis process eosinophils in inflammatory cell clusters and foci of nonspecific pneumonia were determined at approximately the same rate (12.0 % and 19.0 %, respectively in groups 3 and 4, when the FCT – 0.0 % to 20.0 % and in the groups 1 and 2) (see Table 1, 2). That is, if a high activity of inflammation of FCT the eosinophils in the concrete undetectable in sites of nonspecific inflammation in the lung tissue, when tuberculomas, regardless of the degree of specific activity of inflammation, they were detected in similar areas.

Only in one case among patients with tuberculoma of the third group – with a high degree of specific inflammation activity, there is a very large number of eosinophils in the various structural elements of lung tissue: in the capsule of tuberculoma, in the foci of specific pneumonia, in the alveolar septa and fibrous strands, and also (in moderate amounts) in the alveolar exudate, – which could be a reflection of the body's allergic predisposition of the patient (anamnesis patient noted an allergic reaction to some anti-TB drugs, in particular – to gatifloxacin).

Thus, when the secondary forms of pulmonary tuberculosis with long undulating course (fibro-cavernous tuberculosis, tuberculoma), eosinophils were present in the foci of tuberculosis process with a high degree of activity in the majority of patients, indicating about their active participation in the specific inflammation.

Conclusion

1. In patients with fibro-cavernous pulmonary tuberculosis (FCT) and tuberculomas detection rate of eosinophils in the structures of the cavity / tuberculoma, as well as specific inflammation foci (foci dropout, granulomas, foci of specific pneumonia) is directly related to the high activity of tuberculous process.

2. With a high degree of activity of tuberculous inflammation in patients with FCT eosinophils in the lung tissue detected in all cases (100 % versus 45 % for inactive tuberculosis inflammation, p <0.05), with localization in all layers of the wall of the cavity (granulation layer, on the border with necrosis, in the fibrous layer – a total of 108 % versus 0 % with inactive inflammation, p <0.05) and specific structures (foci of dropout near caverns, granulomas, foci of specific pneumonia, respectively – in 80 % of patients versus 15 %, p <0.05), – which indirectly indicates the possible bactericidal and fibrosis-stimulating action of eosinophils.

3. By reducing the activity of inflammation in cases of FCT eosinophils often defined in the centers of nonspecific pneumonia and inflammatory cell clusters (20.0 % versus 0.0 %, with the active FTC, p <0.05), and also tend to be detected in fibrotic formations of lungs (fields of fibrosis, fibrous strands: 35 % versus 12 % at active FTC, p = 0.066), – that reducing the activity of tuberculosis with partial «healing» and limitation of inflammation, probably reflects positive trends (not excluded, as fibrosis-stimulating).

4. With a high degree of activity of tuberculous inflammation in patients with pulmonary tuberculomas, as well as at the FCT, eosinophils are found in all cases (100 % of patients versus 33 % for inactive tuberculosis inflammation, p <0.05), with preferential localization in the wall of the capsule of tuberculoma (granulation layer, on the border with necrosis – a total of 108 % versus 33 % for inactive tuberculosis inflammation, p <0.05) and in the dropout foci near capsules, granulomas, foci of specific pneumonia (respectively at 64 % of patients versus 19 % p <0.05), except of the fibrous layer of tuberculoma where eosinophils are present regardless of the activity of inflammation (respectively 64 % and 57 % of patients with tuberculomas, p> 0.05, versus 44 % and 0 % of patients with FCT, p < 0.05) – which, in contrast to the FCT, this layer capsules may be due to their constant activity (it is possible, stimulating fibrosis).

5. At low activity of specific inflammation in patients with pulmonary tuberculomas (as opposed to inactive forms of FCT) eosinophils present in sites of nonspecific inflammation in the lung tissue (in foci of nonspecific pneumonia, inflammatory cell clusters), – reflecting the peculiarities of the course of this form of pulmonary tuberculosis.

6. The presence of eosinophils in the foci of activity of tuberculosis process in the majority of patients with secondary forms of pulmonary tuberculosis with long undulating course (fibro-cavernous tuberculosis, tuberculoma) testifies to their active participation in the specific inflammation, probably aimed at the destruction of alien organisms (mycobacteria) and in processes of fibrosis formation.

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