

A Contemporary Review on Eosinophilia

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It was believed that in classical Unani text that there was no concept of eosinophilia in the ancient time. On the contrary, while going through the Unani literature, it was revealed that renowned Unani scholars have described certain diseases like *Zeequn Nafas* (Asthma), *Deedan-e-Ama* (Intestinal Worms), *Daulfeel* (Elephantiasis), *Nar-e-farsi* (Eczema) and *Jarb* (Scabies) in their treatises, which are well known causes of eosinophilia. Moreover, there are some conditions namely *Sual* (cough), *Attas* (Sneezing), *Hikka* (Pruritus), *Hikkaul unf* (Nasal itching) and *Shara* (Urticaria), which reflect the concept of allergen in their etiology and management.

The invention of microscope played the vital role in the discovery of eosinophils. Thus, diseases which have been described since antiquity mimic with the eosinophilia, and a stepwise progression in knowledge has led to the present era as a well known clinical entity viz. Eosinophilia.

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Eosinophilia refers to an increase in the number of eosinophilic leucocytes above normal ($>0.7 \times 10^9/L$) levels if calculated from the total leucocyte and differential count and more than about $0.2 \times 10^9/L$ if determined by absolute counting methods¹.

The life span of eosinophils is much longer than neutrophils, and unlike neutrophils tissue eosinophils can re-circulate too. During most infections, eosinophils are not important. However, in invasive helminthic infestations, such as hookworm, schistosomiasis, strongyloidiasis, toxocariasis, trichinosis, filariasis, echinococcosis, and cysticercosis, they play a central role in host defence. And also associated with bronchial asthma, cutaneous allergic reactions, and other hypersensitivity states².

Since last three decades there has been renewed interest in the eosinophil related diseases mainly due to the advancement to conduct

in-depth cell analysis, immunologic and biochemical techniques. These studies have favoured two hypotheses of the function of the eosinophils as a homeostatic modulator of inflammation, serving to suppress the immunoinflammatory reaction and prevent its excessive spread. Secondly, the role of eosinophils in host defence because of an ability to kill invasive metazoan parasites. These are not the only hypotheses for eosinophil function, but these are the two evidence based theories³ as a result of their potential role in asthma, helminthic parasite infection. However, it may cause tissue damage when inappropriately activated eosinophils remains intact⁴.

The concept of eosinophilia in Unani System of medicine seems to be relatively new. But the historical genesis of this disease indicate that the basic concept is an ancient one. Most of the famous Unani scholars have described the diseases such as *Zeequn Nafas* (Asthma), *Deedan-e-Ama* (Intestinal Worms), *Daulfeel* (Elephantiasis), *Nar-e-farsi* (Eczema) and *Jarb* (Scabies) in their treatises. They have mentioned the etiological factors and clinical features of these diseases which are almost similar to related-diseases eosinophilia occurring due to various etiologies.

In Tibb-e-Unani, eosinophilia is not as such reported but it may be inferred in terms of *Sual* (cough), *Attas* (Sneezing), *Hikka* (Pruritus), *Hikkaul unf* (Nasal itching) and *Shara* (Urticaria). In context of *Zequn Nafas* (Asthma) most of the Unani scholars have acknowledged dust particles and smoke as the causative factors. In the same way, as some foods responsible for causing the *Shara* (Urticaria).

It is obvious that proper equipments (microscope) and technologies to diagnose the eosinophilia were not available at the time of ancient Unani Physicians. The only way to diagnose a disease was experience and observations. That's why they could not describe this cellular derangement so precisely.

As written by Hippocrates (460- 377 B.C.) in *Abizeemia* that worms developed mostly in the season of *kharif* (autumn)⁵. It shows the seasonal variation of symptoms of eosinophilia is linked to helminthic infestation.

Galen (132-201 A.D.), in his book *Kitabul Alamat*, has described the symptoms of worms infestation as decreased appetite, weakness, nausea, and dry cough. *Hayyat* (Ascaris) are not only common in children but also more in them in comparison to older ones⁶.

Among Arabs, Ali Bin Rabban Tabri (810-895 A.D.) was the first physician who described *Kharish* (itching) as parasitic disease in his famous book *Moalijat-e-Buqratia*⁷.

Rhazes (865-925 A.D.), in his book *Kitabul Mansoori* has cited the clinical features of *Zukam* (Coryza) as irritation and itching in nose and sneezing. In context of *Daulfeel* (Elephantiasis), has been recognised

as swelling of lower limb with muddy colour and development of varicose veins⁸. In *Kitabul Hawi*, Rhazes has mentioned dry cough as the symptom of *Deedan-e-Mustadir* (round worms). While classifying the types of worms, under the heading of *Alamat* (symptoms), and quoted headache, vertigo and episodes of epilepsy similar to the clinical features of neurocysticercosis⁵.

Avicenna (980-1037 A.D.), in his book *Al-Qanoon Fit Tib* has mentioned smoke among the causes of *Zeequn Nafas* (Asthma). In context of *Attas* (Sneezing), he has advised to abstain from dust and smoke to prevent it. While writing the symptoms of worms, he has quoted breathlessness and difficulty in speech (dysarthria). It reveals that Unani Scholars had the concept of neurocysticercosis but could not explain it due to lack of technology. Under the heading of *Alamat* (symptoms) of worms oedema of body and swelling of testes, resembling the signs of filariasis and has been documented. While illustrating about cough, dust particles and smoke in the etiological factors were also described. It is noteworthy that he has explained about seasonal variation in the intensity of cough also revealed ingestion of *Ghaleez aur Raddiul kemoos* (heavy and adulterated) food as one of the causes of *Hikka* (Pruritus), that reflects the concept of allergy or hypersensitivity to food⁹.

Ismaeel Jurjani (12th century A.D.), in his book *Zakhira-e-Khwarzam Shahi* has enumerated one primary and nine secondary causes of *Zeequn Nafas* (Asthma). In secondary causes he has listed smoke and ingestion of cold things. While citing the causes of *sufra* (cough), inhalation of noxious substance like dust has also been reported. *Deedan-e-Ama* (intestinal worms), the clinical features like gastric irritation, intestinal cramps and loose stool has been cited. It is noteworthy that he also revealed that, when worms affect lungs it causes dry cough which is presently described as Loffler's syndrome¹⁰.

Najib al-din Samarqandi (d. 1222 A.D.) described *Sara Deedani* (parasitic epilepsy) under the heading epilepsy that occurs due to intestinal worms because bad, toxic and purulent fluid and vapours from these worms reach brain and causing discomfort leading to spasm and abnormal activities of brain¹¹.

Hakeem Azam Khan (1813-1902 A.D.) in his book *Akseer-e-Azam* has recognised *Sara* (epilepsy) and *Khafqan* (palpitation) as the complications of intestinal worms. Under the heading of method of diagnosis, *Sara* (epilepsy), *Ghashi* (syncope) and *Warm-e-Khusien* (Orchitis) were mentioned in the clinical presentation of intestinal worms with dry cough in case of *Hayyat* (*Ascaris*)¹².

Hakeem Ajmal Khan (1868-1927 A.D.) wrote two types of *Zeequn Nafas* (Asthma), dry and wet. In dry asthma, only spasm of bronchioles occurs while in wet it is accompanied by accumulation of

phlegm. According to him, intestinal worms are of three types and nausea and vomiting are their important symptoms¹³.

In the 18th century Leeuwenhoek discovered the microscope and observed Giardia in his stool for the first time¹⁴ and laid the foundation in the discovery of micro-organisms.

In 1846, Wharton Jones for the first time described unstained eosinophils. The discovery of the eosinophil was announced by Paul Ehrlich in a presentation to the physiological society of Berlin on 17th January 1879, in the paper entitled "Contribution to knowledge of granulated connective tissue cells and of eosinophil leucocytes" as following:

The most important of these granulations by far is the eosinophil or alpha granulation.

Ehrlich found eosinophils in large numbers in bone marrow, leading him to speculate that they might be produced at this site. Opie examined in 1904 animals infected with *Trichinella spiralis* and observed that eosinophils tend to surround the lymph nodes of the carriers. Schlecht and Schwenker in 1912 discovered that guinea pigs which survive anaphylactic shock developed massive peribronchial eosinophilia 24 hours later. In 1915, Weinberg and Seguin determined the possible presence of antigen in eosinophils¹⁵.

Subsequently in the year 1932, Jadassohn, put forward a theory that eosinophilia must not be considered proof of anaphylactic disease. He believed that local eosinophilia, intravascular and perivascular, of comparative intensity could be due to the non specific changes. He mentioned possible changes in electrostatic potential after injection of histamine, atropine, pilocarpine or morphine¹⁵.

Loeffler first identified the association between pulmonary infiltrates and eosinophilia in 1932. Loeffler first described a clinical syndrome characterized by mild respiratory symptoms, peripheral blood eosinophilia and transient migratory pulmonary infiltrates. In the original series of Loeffler, most of the patients with simple pulmonary eosinophilia likely had Ascaris infection. Crofton in the year 1933, classified the eosinophilic pneumonias into five groups on the basis of clinical criteria namely Loeffler's syndrome, prolonged pulmonary eosinophilia, pulmonary eosinophilia associated with asthma, tropical eosinophilia and periarteritis nodosa¹⁶.

Tropical pulmonary eosinophilia (TPE) was first described in the early 1940s as a syndrome characterized by fever, malaise, anorexia, weight loss, paroxysmal dry cough with dyspnoea or wheezing, marked peripheral blood eosinophilia and spontaneous resolution over several weeks' time. In 1943, Tropical eosinophilia was first identified as a

syndrome characterized by severe spasmodic bronchitis, leucocytosis and high blood eosinophilia. Simultaneously tropical eosinophilia was described by Weingarten and subsequently incorporated into Crofton's original classification of pulmonary eosinophilia. Campbell in the same year suspected that sulfhydryl groups and disulfide bonds in *Ascaris* keratin might account for its ability to induce pronounced eosinophilia¹⁷.

In the 1950s and 1960s, filarial infections were recognized as the cause of eosinophilia²². Esselier in 1951 administered to himself intravenously a suspension of larvae of *Ascaris suis* and developed within days classical symptoms of Loeffler's syndrome¹⁵.

Tschumy in 1958 established the association between inhalation of smoke and pulmonary eosinophilia. In the year 1960, Christoforidis and Molnar identified the first patient with chronic eosinophilic pneumonia (CEP). In 1961, Sunderman and Sunderman described that inhalation of nickel fumes are among the toxic chemicals that have been reported as causing multiple pulmonary nodules on the chest radiography and a peripheral blood eosinophilia. In later years, Ford described drug-induced pulmonary eosinophilia¹⁸.

In the year 1968, *Idiopathic hypereosinophilic syndrome* (IHS) a rare disorder firstly described by Hardy and Anderson. In the next year, chronic eosinophilic pneumonia (CEP) was described as a clinical entity by Carrington and Coworkers. They were also the first to describe series of patients with chronic eosinophilic pneumonia (CEP)¹⁹. Chronic eosinophilic (1969) pneumonia was individualized as a distinct entity by Carrington and colleagues, who described a series of 9 patients with detailed clinical, radiologic, physiologic and pathologic data²⁰. In the same year 1969, Leibow and Carrington broadened the description of the term eosinophilic pneumonia to include all disorders characterized by infiltration of the lungs with eosinophilia, with or without an excess of eosinophils in the peripheral blood¹⁶.

In later years 1980, Fox and Seed described a chronic eosinophilic pneumonia which is characterized by pyrexia, cough, dyspnoea and malaise accompanying widespread bilateral shadowing of the chest on the chest radiograph. In 1982 Halonen et al, highlighted a significant relationship between serum IgE level and Eosinophilia in population presumed to be free of parasite where IgE presumably provide a better clue to atopy than do skin test¹⁸.

In 1988, Gaenster and Carrington noted classic pattern of "Photographic Negative or reversal of the shadow usually seen in pulmonary oedema" as evocative of Idiopathic Chronic Eosinophilic Pneumonia. In the next year, idiopathic acute eosinophilic pneumonia was first recognized as a unique clinical entity. In the year 1989, Eosinophilia-Myalgia syndrome was described in New Mexico²¹.

Wasserman in the year 1989 described that mast cells contain or can synthesize multiple mediators of immune and inflammatory responses: histamine, prostaglandins, leukotrienes, platelet activating factor, proteases and other lysosomal enzymes and materials affecting chemotaxis of eosinophils and neutrophils²². In the same year Eosinophilia-Myalgia syndrome was described in New Mexico. Over 1500 cases were reported over the next 2 years, with over 30 deaths²³. Later on, there was a report that eosinophils were cytokine producing cells, and generate transforming growth factor alpha (TGF- α)²⁴.

In 1994, Hayakana and colleagues reported large case series include 13 patients of Acute Eosinophilic Pneumonia (AEP)²⁵. Pope-Harman and colleagues in 1996 described 15 patients of AEP²⁶. In 1997, Di Lorenzo *et al.*, reported that there is an inter relationship of the allergen type, total serum IgE, eosinophil and bronchial hyper responsiveness suggesting that all three may play a role in the development of bronchial asthma in rhinitis patient²⁷.

In 2000 S.V. Joshi *et al.*, observed that specific IgE for house dust mite and total serum IgE play an important role in triggering exercise induced asthma²⁸.

In the year 2001 Alic Verghese *et al.*, reported significantly raised IgE levels in all asthmatic groups. However, increase in the total IgE level is secondary to other changes in the inflammatory pathway²⁹.

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