Perspective

Leukemoid Reaction: Unusual Causes

Anwar ul Haque and Noor ul Aan

Increased neutrophils are considered to be indicative of acute bacterial infection. Not always true. Neutrophils are almost normal “flora” of PAP smears sometimes misinterpreted as “acute inflammatory”. We have yet to see a single PAP smear devoid of neutrophils. We believe cervical mucin is strongly chemotactic for the neutrophils and hence they are always there; perhaps as preventive measure!

Acute myocardial infarction contains numerous neutrophils after initial insults. Certainly it is not acute myocarditis. Fine Needle Aspiration Cytology (FNAC) of malignant tumors may yield numerous neutrophils signifying that tissue necrosis is an important causes of neutrophils invasion and their presence; not necessarily related to infections.

Tuberculosis which is always taught as chronic granulomatous inflammation in basic pathology courses, usually contains numerous neutrophils in initial acute stage as well as in recurrences. Very few lymphocytes are seen. A few epithelioid cells and caseous necrosis are the clue to the diagnosis.

On the other hand paradoxically in overwhelming infections neutrophil count may go down due to marked consumption of these brave soldiers!

Overwhelming post splenectomy septicemia with Disseminated Intravascular Coagulation (DIC) is an example of this condition. Some bacterial infections such as typhoid may be associated with low neutrophil counts perhaps due to suppressive effect on bone marrow.

Fungal infections are generally considered as “Chronic Granulomatous Inflammation” and are associated with high lymphocyte count. However certain fungal infections such as mucormycosis may be associated with very high neutrophil counts in the form of leukemoid reaction. Not keeping this possibility in view will deprive the patient due treatment and may lead to death.

We recently encountered two cases where leukemoid reactions were associated with 1) systemic mucormycosis and 2) Metastatic mucinous adenocarcinoma of lung origin(Figure 1). Our intent is not to describe those cases here in any significant detail but just to alert the physicians about unusual possible etiological factors in causation of leukemoid reaction.

1) Leukemoid Reaction in Disseminated Systemic Mucor Mycosis: A 40 year old otherwise healthy woman who had hitherto undiagnosed bicuspid aortic valve developed sudden abdominal pain and marked skin tenderness.

Her neutrophil counts were in the range of 80,000. Just prior to her death a skin biopsy revealed disseminated mucormycosis causing extensive necrotic changes in the skin.

2) Leukemoid reaction in a Primary Lung Mucin Adenocarcinoma with subtle metastases to the bone marrow and spleen: A 55 yrs old male patient presented to General medicine. His active complaints were cough, breathlessness, malaise, fatigue, weight loss and hepatosplenomegaly. His baseline investigation showed leukemoid reaction with white blood cell count reaching up to 100,000/µl with more than 80% neutrophils. His bone marrow was hyperplastic with increased LAP score. His spleen FNAC and the bone marrow contained a few atypical mucin producing individual cells!

In the first case mucormycosis and in the second case metastatic individual mucin producing cells were considered to be the etiological factor for leukemoid reaction!

Discussion

Leukemoid reaction is defined as the increase in total number of leukocytes; more than 500 X 10^9/L. It is characterized by blasts, promyelocytes, myelocytes, and metamyelocytes in the peripheral blood. Leukemoid reaction is usually seen in response to infection, inflammation, or in response to some other
therapeutic agents such as growth factors. It is less commonly caused by malignancy. (Table 1)

**Table: 1 Common and Usual causes of Leukemoid reaction:**

| Infection (most common cause) |  
|-----------------------------|--
| Pneumonia, bacterial |  
| Acquired Immune deficiency (AIDS/HIV) |  
| Trichinosis |  
| Disseminated Tuberculosis |  
| Visceral larval migrans |  
| Pertussis |  
| Acute infestation of Trichinella |  
| Malaria |  

**Inflammation:**
- Empyema
- Pneumonia

**Malignancy**
- Myeloproliferative disorders
- Hodgkin lymphoma typically causes mild-to-moderate neutrophilia

**Myeloproliferative disease**

**Hypereosinophilic syndrome**

**Some solid tumors**
- carcinoma of the lung, stomach, pancreas
- Splenectomy undifferentiated carcinoma
- Decreased egress of neutrophils from circulation
- Administration of corticosteroids
- Decreased neutrophil margination, steroid administration
- exercise
- epinephrine administration
- other stressful situations (e.g., trauma, severe pain)

**Increased release of neutrophils from marrow:**
- infection
- stress
- hypoxia

A mutation in the CSF3R gene

**Therapeutic repetitive injections of pegylated G-CSF or G-CSF—**

Neutrophil recruitment and activation is considered as the main innate immune response against microbial and viral infections. It is the most important leukocyte in typical inflammatory reaction. In the process of recruitment of leukocytes to the site of infection and injury, first neutrophils are marginated, rolled, adhered to endothelium and then migrated across the endothelium and vessel wall. This is followed by migration into the tissue towards a chemotactic stimulus. Multiple growth factors, adhesion molecules, and cytokines factors are involved in the journey of neutrophils from bone marrow to target organ. Tissue macrophages, mast cells, and even endothelial cells when injured respond by secreting several cytokines, including TNF, IL-1, and chemokines. The local effect of TNF is to activate the leukocytes and to increase the production of other cytokines. TNF also act systemically and causes leukocytosis.

Inaba et al proposed that cancer cells produced mucin, which attracted and activated the macrophages through the Macrophage Scavenger Receptor. This mucin also induces the expression of Cyclooxygenase enzyme (COX-2) in these macrophages. COX 2 converts the Arachidonic acid, a cell membrane phospholipid, into different Prostaglandins. Prostaglandin E2 secreted from the macrophages boosts the Prostaglandin E2 production from macrophages itself via a positive feedback and also from the nearby cells. PGE2 causes vasodilatation and increases the permeability of post capillary venules.

**Table: 02) Unusual causes of Leukemoid Reactions**

| Mucormycosis | Metastatic mucinous carcinoma |

To summarize, mucin activates macrophages which secrete Prostaglandins and Tumour Necrosis Factor (TNF). These two cause increased vascular permeability and pool the leukocytes to the site of mucin production and also in the blood circulation.

Here we are proposing that in both cases mucin was the agent which had attracted neutrophils to the circulation and in the tissue as well. Mucin liberated from metastatic mucinous adenocarcinoma cells and mucin of mucormycosis attracted neutrophils in the blood stream.

**References**