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Leukocytosis- A tight roped walk

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ABSTRACT

It is common for patients to reveal a leukocytosis (increased white blood cell count) within twenty four hours of initiation of a glucocorticoid. It is important for clinicians to be aware of this expected side effect and to understand the rationale for such an increase. Here, we present a case of nine years old boy with intracranial space occupying lesion (medulloblastoma) posted for surgery who was on oral steroids and had leucocytosis which gradually subsided on stopping steroids.

Keywords: Steroids, glucocorticoids , dexamethasone, white blood cell, neutrophils.

Drugs can induce almost the entire spectrum of hematologic disorders, affecting white cells, red cells, platelets, and the coagulation system [1]. Common drugs responsible for causing leukocytosis are glucocorticoids, beta agonists, lithium and anti-epileptics [2]. Glucocorticoids (e.g. dexamethasone, methyl-prednisolone, prednisone) are known to increase the white blood cell count upon their initiation. The increase in white blood cell (WBC) count is primarily contributed from neutrophils. Leukocytosis is first noted after a few hours of administration and reaches maximal intensity within two weeks of continued treatment after which the WBCs decrease but not to the pre-treatment level. The pattern of steroid induced changes in the total white blood cell, neutrophil, lymphocyte and eosinophil count is predictable during the first three days of initiation of treatment in absence of active infection. Although the degree of leukocytosis may be related to the dosage administered, it may appear sooner with higher doses.

The peripheral smear helps in differentiating steroid induced leukocytosis from that caused due to infection. During infection, unsegmented or band neutrophils are released from the bone marrow resulting in: 1) Shift to the left in the peripheral white blood cells, i.e., more than 6 percent band forms and 2) Appearance of toxic granulation. These findings are rare in corticosteroid induced leukocytosis [3,4]. Keeping these things in mind will help clinicians avoid unnecessary medical work-up for other conditions and avoid patient exposure to additional drug therapy that is not warranted, such as intravenous antibiotics.

CASE REPORT

A nine years old boy was symptomatic since last one and a half years with complaints of headache, vomiting and instability while walking, with an increase in both intensity and frequency of the symptoms for last two months. In view of CT scan and MRI showing intracranial space occupying lesion (Medulloblastoma) and hydrocephalus, he was started on acetazolamide, dexamethasone, domperidone and paracetamol. After taking one week of these medications, he was admitted in the hospital for surgery.

On admission, patient was afebrile, and his vitals were stable. Mild ataxia was present with no neurological deficit. On laboratory investigations, his total leucocyte count was 14800/mm^3.

Table 1 – Serial Hemogram of the patient

Test / Day of admission	1st	2nd	4th	5th	7th	8th	9th	10th	12th
Hb (gm%)	13.6			13.4	11.6	10.8	11.9	11.7	12.2
WBC (cells/cmm)	14800	15900	16400	21400	36000	22000	17600	14700	12400
Platelets (/cmm) in lacs	4.32			3.54	2.42	2.11	2.05	2.42	3.75

Other investigations including blood sugar, liver and kidney function tests and coagulation profile were normal. Patient was started on intravenous ceftriaxone after sending samples for blood culture, urine routine and microscopy and CRP. The next day WBC count was 15,900/mm3; however, CRP was negative and urine examination was normal. Blood culture showed no growth after 72 hours of incubation. His viral markers including HIV and HbsAG were also negative. Patient was clinically stable with no fever or any other symptoms. His WBC counts on subsequent days increased to 16,400/mm3 and 21,400/mm3.

Patient was taken for surgery with the surgeon changing the antibiotics to intravenous ceftazidime and netilmicin. His surgery was uneventful and the next day following surgery, counts further increased to 36,000/mm3. Repeat samples for CRP and procalcitonin were sent, which were within normal limits. With surgeon's consent intravenous dexamethasone was stopped. The WBC counts decreased to 22,000/mm3 the next day. Subsequently the counts showed decreasing trend as shown in the table 1. The patient was discharged after a normal post operative period.

DISCUSSION

The WBC count normally drawn from a patient is made up of a number of different leukocytes, which includes 60-70% neutrophils, 28% lymphocytes, 5% monocytes, 2-4 % eosinophils and 0.5% basophils [5]. When a WBC count is done on a patient, the laboratory value reflects the leukocytes distributed within the blood and not those in the bone marrow, tissue or attached to the endovascular lining of blood vessels. It is evident that the neutrophils make up the greatest amount of leukocytes in the total white blood cell count and thus can have the greatest impact on changes in the WBC count [6]. They are initially released from the bone marrow as immature neutrophils that are characterized as having a non-segmented, band like appearing nucleus, also known as "bands".

An increase in the number of these immature neutrophils in circulation can be indicative of a bacterial infection for which they are being called to fight against. This is normally seen or called a "left shift" in a white blood cell differential [6]. As the immature neutrophils become activated or exposed to bacterial pathogens, their nucleus will take on a segmented appearance. These and other neutrophils can be found in several compartments within the body, but the two compartments that relate to the importance of this case report are the marginal compartment (those neutrophils attached to the endothelium of the blood vessel) and the circulating compartment (those circulating in the blood vessels along with other cells).

All of this information is important for the proper interpretation for the reasons that the WBC count has increased, especially when glucocorticoids (e.g., dexamethasone, methylprednisolone, and prednisone) are being given. It is well known that glucocorticoids cause increase in the WBC counts. Upon further evaluation of the increased WBC count, it is the neutrophils that contribute the most to the increase. The causes for glucocorticoid induced increase in WBCs include demargination of neutrophils from the endothelial surface of blood vessels, delayed transmigration of neutrophils into the tissue, delayed apoptosis, and an increase in the release of neutrophils from the bone marrow. While all of these contribute to the increase in circulating neutrophils seen on a WBC count, they do so at different degrees with demargination being the predominate effect [7,8,9].

There are 3 major mechanisms responsible for corticosteroid induced granulocytosis:

1. Demargination of neutrophils from endothelial cells (60% of the rise): L-selectins are present in leukocytes that mediate their rolling on the endothelial lining of the vessels. This relies on the balance between removal of L-selectins from cell surface by the enzyme cysteine-metalloproteinase (sheddase) and production of new L-

selectins by the neutrophils. Steroids inhibit L-selectin synthesis at gene level, leading to demargination of leukocytes into the circulation.

2. Delayed migration of neutrophils into tissues and rate of apoptosis (30% of the rise): During rolling, integrins are activated on the surface of leukocytes which bind to the ICAM-1 and PECAM-1 on the endothelial surface resulting in adhesion and trans-migration of leukocytes through the endothelial cells. Steroids down-regulate all these molecule, and the leukocytes are bound to stay in the circulation. Also, by unknown mechanism steroid inhibit apoptosis of leukocytes, prolonging their survival period.

3. Release of non-segmented (band) neutrophils from bone marrow (10% of the rise).

A reactive leukocytosis, typically in the range of 11,000 to 30,000 per mm^3 can arise from a variety of etiologies. Any source of stress such as surgery, exercise, trauma, burns and certain medications such as corticosteroids are known to increase the total leucocyte count [10]. A case reported by Meilin Weng et al on corticosteroid induce leukocytosis during the pain management stated that leukocytosis can be induced even by a small dose of corticosteroids. This steroid-induced neutrophilia can be distinguished from neutrophilia due to an acute infection by the lack of increased proportion of band forms, and lack of the development of morphological changes such as toxic granulation, Dohle bodies, and cytoplasmic vacuoles [11]. A case reported by Simeon Barker et al showed monocytosis accompanying the neutrophilia in corticosteroid use with a rapid increase in leukocyte numbers with delayed but parallel increase in monocytes, and their resolution on corticosteroid withdrawal [12].

CONCLUSION

While it is important to know the degree of increase in white blood cell counts, it is just as important to be able to appropriately assess the white blood cell differential, so as to avoid missing a treatable condition. Glucocorticoid induced leukocytosis is generally not associated with increase in temperature or worsening in the condition that is being appropriately treated. Therefore, it is important for the clinician to put all of these factors in context when assessing, monitoring and treating the patient's medical condition.

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