

chronic idiopathic neutrophilia (CIN)

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Female presented for the first time at the age of 24 years for a persistent neutrophilia without clinical symptoms.

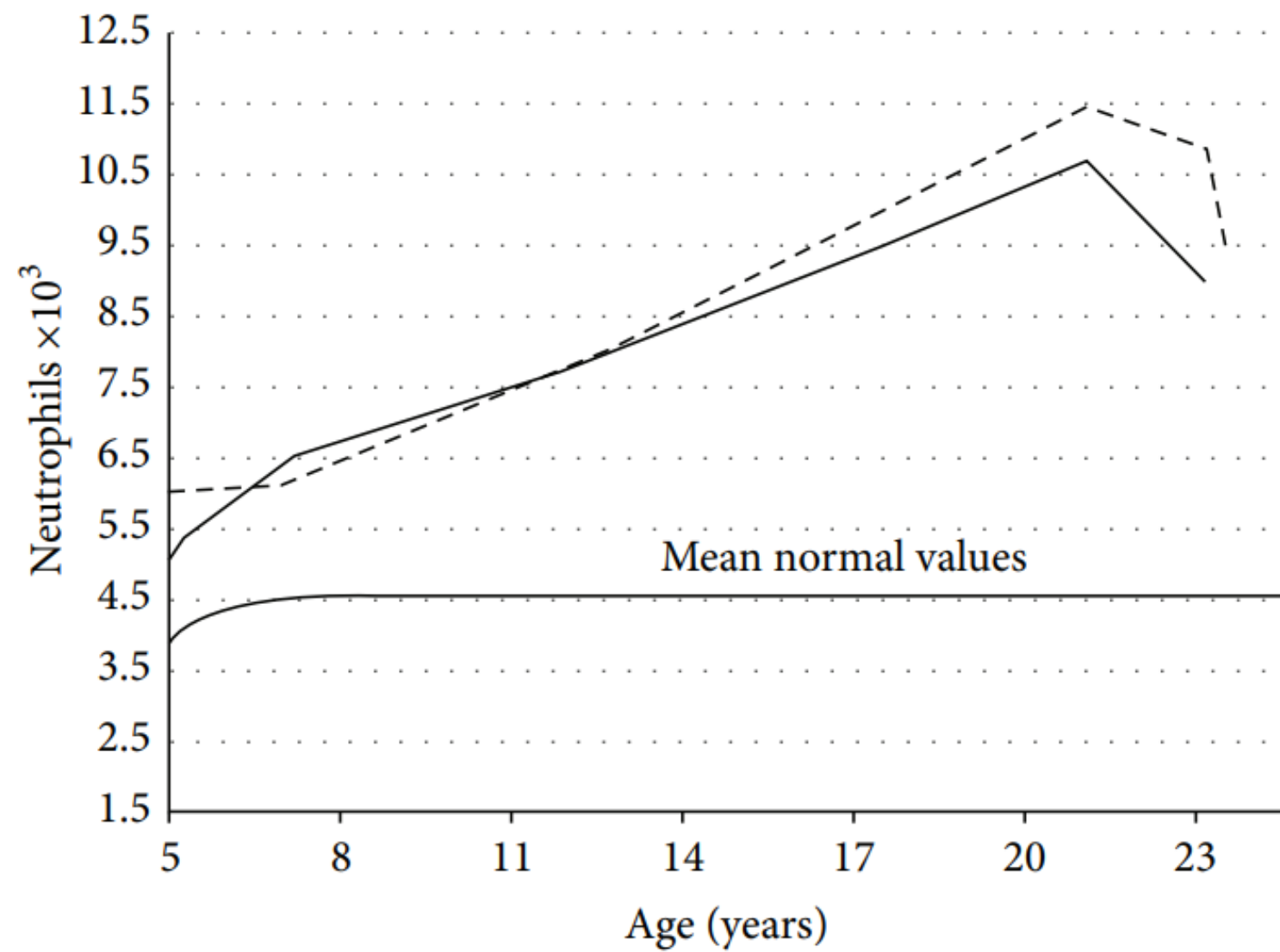
Since the early years of life till the age of 9 ,neutrophil leukocytes at the complete blood count, performed every year, have been higher compared to the average reference values for age; thereafter they have further increased to a true neutrophilia (more than 2SD from mean values for age).

Granulocyte morphology was normal without immature forms in the peripheral smear.

The other leucocyte subpopulations, red blood cells, and platelets **parameters have remained** normal throughout the period of observation.

Hematologic parameters were normal in parents.

- All causes of neutrophilia  Negative
- The patient has had an **overall good health** during their life; in particular they have never had persistent inflammations or infections;
- she disclaimed prolonged administration of **glucocorticoids or lithium**;
- **spleen size** has always been normal for age; finally she had no other risk factors for neutrophilia such as **obesity and/or smoking**.
- Then, owing to these clinical and laboratory conditions, diagnosis of CIN has been formulated at the time of our observation



- Neutrophilia refer to an increase in the number of neutrophils in peripheral blood.
- Two standards of deviation above the mean has been used as a cut-off which corresponds to about 7700 neutrophils per microliter in adults .
- It is important to note that the cut-off is age dependent as neutrophil count varies with age
- Neutrophil count is elevated at birth and decreases to adult range within a few weeks after birth .

Age	WBC (cells/microL)	ANC (cells/microL)	Percent neutrophils (approximate)
Fetus >30 weeks	7710 (range 2720 to 12,700)		23% of nucleated cells including nucleated RBCs
Birth	18,100 (range 9000 to 30,000)	11,000 (range 6000 to 26,000)	61% of WBCs
24 hours	18,900 (range 9000 to 34,000)	11,500 (range 5000 to 21,000)	61% of WBCs
1 week	12,200 (range 5000 to 21,000)	5500 (range 1500 to 10,000)	45% of WBCs
1 month	10,800 (range 5000 to 19,500)	3800 (range 1000 to 9000)	35% of WBCs
1 year	11,400 (range 6000 to 17,500)	3500 (range 1500 to 8500)	31% of WBCs
10 years	8100 (range 4500 to 13,500)	4400 (range 1800 to 8000)	54% of WBCs

- Some common etiologies include; infection, inflammatory conditions, myeloproliferative disorders, malignancies, endocrinopathies, drugs, and anemia.
- Rare disorders such as LAD

- In some cases, however, there is **no apparent cause** that explains the elevated neutrophil count.
- The term chronic idiopathic neutrophilia (CIN) is used to *refer to an elevation of neutrophil count that persists for months or even years with no clear underlying cause in an otherwise asymptomatic patient* .

- Certain conditions such as stress, exercise, smoking, obesity, and obstructive sleep apnea have been associated with CIN and may provide explanations for neutrophilia previously thought to be idiopathic.

- فقدان یک رویکرد سیستماتیک برای ارزیابی به طور بالقوه می تواند منجر به هزینه های پزشکی گزاف و قرار دادن بیماران در معرض آزمایش ها و روش های پزشکی غیر ضروری شود.

Table 1. Diagnoses of patients presenting with chronic neutrophilia (n = 134)

Diagnosis	No. patients
Chronic idiopathic neutrophilia	57
Neutrophilia lasting <6 mo	29
Chronic infection	4
Post splenectomy	7
Myeloproliferative neoplasm with neutrophilia	20
Neutrophils $<8000 \times 10^6/\text{L}$	9
Chronic myeloid leukemia	3
Prednisone/lithium use	5
Total	134

Neutrophils in CIN

- Peak neutrophil counts ranged from 8.9 to 22.6 $\times 10^9$ /L.
- The mean neutrophil count on presentation was 9.448 .
- When patients presented with acute infections, they experienced additional elevations in their neutrophil numbers, settling back down to a chronically elevated level when the infections subsided.
- The mean duration of neutrophilia identified in these patients was 7.3 years with a range of 1 to 21 years.

Other Blood Elements in CIN

- **Erythrocytosis** was present in five patients.
- Three of these had documented carbon monoxide levels of 8-9%.
- Of the other two, one was chronically hypoxic, and the other patient's evaluation strongly suggested secondary polycythemia.

- Drug Exposure in CIN
- Coexisting Illnesses in CIN  NO

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Patient	Age at presentation, y	Race	Sex	Duration, y	Total neutrophils at presentation ($\times 10^9/L$)	Peak neutrophils ($\times 10^9/L$)	Drugs	Psychiatric diagnosis	Smoker BMI, kg/m ²

Conditions associated with CIN and their proposed mechanisms




- The following conditions have been associated with persistent neutrophilia; however, the actual causal relationship remains unclear.

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1. Exercise

- neutrophilia associated  with exercise especially intense exercise .
- Exercise is thought to play a role in promoting neutrophilia by causing  de-margination of neutrophils from endothelial walls mediated by catecholamines as well as from the bone marrow under influence of cortisol .
- Exercise has been shown to increase the concentration of circulating neutrophils by 26% .
- Exercise may also induce tissue damage which can trigger systemic inflammation which can further contribute to the neutrophilia

2. Stress

- Stress is the external or internal perturbation of the state of homeostasis of an organism .
- Psychosocial stress  induce neutrophilia .
-  proliferation of hematopoietic stem cell progenitors ,
- an environment of chronic stress  the sympathetic nervous system produced excess norepinephrine which through the beta-3 adrenergic receptor resulted in decrease of C-X-C motif chemokine 12 (CXCL12) levels. CXCL12 plays a key role in signaling involved in the retention of neutrophils in the bone marrow.

3. Cigarette

- smoking It has been long established in human studies that cigarette smoke causes increase in circulating peripheral blood neutrophils, but this is often an overlooked etiology in the workup for neutrophilia .
- Smoking cessation results in normalization of both WBC and ANC, however there is mixed evidence about how long it takes to normalize.
- Another study suggested that normalization of counts **takes greater than 5** years . Conversely, other studies suggest that WBC and ANC normalize within 5 years


پس از کشیدن سیگار، گیرنده های دخیل در چسبندگی و مهاجرت نوتروفیل ها کاهش می یابد.

این امر مهاجرت نوتروفیل ها از خون محیطی به بافت ها را محدود می کند و در نتیجه، تجمع نوتروفیل ها را در گردش همراه با نوتروفیلی افزایش می دهد.

علاوه بر این، برهمکنش اجزای ذره ای و گازی دود سیگار با سطوح مخاطی باعث التهاب سیستمیک می شود که مکانیسم دیگری از نوتروفیلی را نشان می دهد.

- Moreover, cigarette smoking stimulates the release of **TNF- α , IL-1, IL-8, and GM-CSF by alveolar macrophages**
- Increased levels of markers of systemic inflammation such as CRP and fibrinogen have been shown to be increased in cigarette smokers .
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4. Obesity

- Several studies have reported an association between obesity and neutrophilia showing that those with a **higher BMI tended to have higher ANC** than those of normal weight .
- demonstrated an association between **weight loss and decrease in neutrophil** and lymphocytes counts .
- There is increasing evidence that obesity is a chronic inflammatory state .
- **Adipose tissue**  produce increased levels of mediators of inflammation like TNF alfa and IL1-6-8.

5. Obstructive sleep apnea (OSA)

- An association between OSA and neutrophilia has been proposed.

6. Thrombosis

- Venous thrombosis, especially acute thrombosis, has been associated with neutrophilia .
- Thrombosis should always be considered in the differential diagnosis of a patient with unexplained neutrophilia, and it may not always be clinically apparent.

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Evaluation of a patient with chronic idiopathic neutrophilia

The goals in evaluating a chronic neutrophilia are two-fold:

- **Identify any underlying disorders** where the diagnosis might lead to appropriate treatment resulting in prolongation of life or an improved quality of life.
- **Minimize the cost** and testing burden for patients who do not harbor such a diagnosis

- Accurate diagnosis always begins with a **complete history and physical**.
- The history and physical should contain pertinent **family and social history**.
- Specifically, one should **look for abnormalities that may indicate inflammation or malignancy** that may be playing a role in persistent neutrophilia.
- One should *make sure that obesity, medications or a history of smoking are not contributing to the persistent chronic neutrophilia.*

Initial evaluation of persistent neutrophilia.

History and Physical Examination including history for age appropriate screening for malignancy

Complete Blood Count

Comprehensive Metabolic Panel, Sedimentation rate, C-reactive protein

Chest X-ray

Other laboratory testing based on identified abnormalities in above assessments

Review of peripheral blood smear by hematologist or pathologist

Repeat Focused history and physical examination, complete blood count, and complete chemistry profile, sedimentation rate and c-reactive protein at 2, 6, and 12 months, and annually thereafter

Table 4. Indications for additional testing in persistent neutrophilia

Abnormalities on history and physical suggesting inflammation or malignancy

Abnormalities on a chest x-ray or chemistry panel suggesting inflammation or malignancy

Abnormalities in the red cell, platelet, monocyte, eosinophil, or basophil counts

Myelocytes or earlier white cell precursors on smear

Abnormalities on blood smear reviewed by a hematologist or pathologist

Change in history and physical, chemistry, or complete blood count testing on follow-up surveillance

Patient without obesity or smoking history

Fluorescence in situ hybridization or polymerase chain reaction testing for bcr-abl mutation for persistent leukocytosis >12 mo, a rise in neutrophil count by >50%, a total neutrophil count >15,000, or presence of myelocytes, basophilia, eosinophilia, or monocytosis

Evaluation by hematologist and possible bone marrow examination if anemia, elevated hematocrit, thrombocytosis, basophilia, eosinophilia, monocytosis, peripheral blasts, or anyone who develops an abnormally low hematocrit or platelet count

- One should obtain **CBC** as the initial step after **the history and PHEX**.
- The longer an elevated neutrophil count remains stagnant and causes no harm, the less likely it is to do so.
- One should pay attention to counts that may indicate inflammation or malignancy.
- *One should review the PBS , not only for elevated neutrophils, but also abnormalities in the erythrocyte, platelet, monocyte, eosinophil, or basophil counts.*
- Myelocytes or earlier white cell precursors on the smear should lead one to additional diagnostic tests toward one of the myeloproliferative neoplasms.
- A hematologist or pathologist should be involved in the blood smear review.

- If **abnormal cells are noted**; or if anemia, elevated hematocrit, thrombocytosis, basophilia, eosinophilia, monocytosis, peripheral blasts or thrombocytopenia are present
- one should proceed to molecular testing and bone marrow aspiration and biopsy.
- In addition to the molecular testing, evaluation of the BMA BMB should include morphology, flow cytometry ,IHC , and cytogenetics.
- Standard chemistry, hepatic, metabolic and inflammatory marker panels should be reviewed.
- One should also obtain a chest x-ray, and, if any anomalies are noted, one

- If no irregularities are noted, one can consider repeating focused history and physical examination, complete blood count, blood smear review and complete chemistry profile at 2, 6, and 12 months and then annually.

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Practice points 1

- • Chronic neutrophilia is a common disorder that may direct one toward serious diagnoses, including myeloproliferative neoplasms and malignancies, or may be associated with benign disorders, or may never be found to have a cause or produce harm.
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Practice points 2

- • The large number of expensive and uncomfortable diagnostic measures used to diagnosis a patient with neutrophilia are available and must be selected wisely in order to minimize physical and financial cost to the patient.

Practice points 3

- • Obesity, cigarettes and medications are commonly associated with benign chronic neutrophilia.

Practice points 4

- If a patient with chronic neutrophilia is asymptomatic and has no abnormal findings on physical examination, routine laboratory testing, chest x-ray, radiology targeted to symptoms and blood smear review by a pathologist or hematologist, it is safe to observe the patient without additional testing unless changes occur.

Practice points 5

- • Additional evaluation with bone marrow aspiration and biopsy and molecular studies should be performed when abnormal blood smears or clinical symptoms warrant.

- This should focus on medications, family and social history, including smoking history and obesity, as well as evaluation for inflammation or malignancy

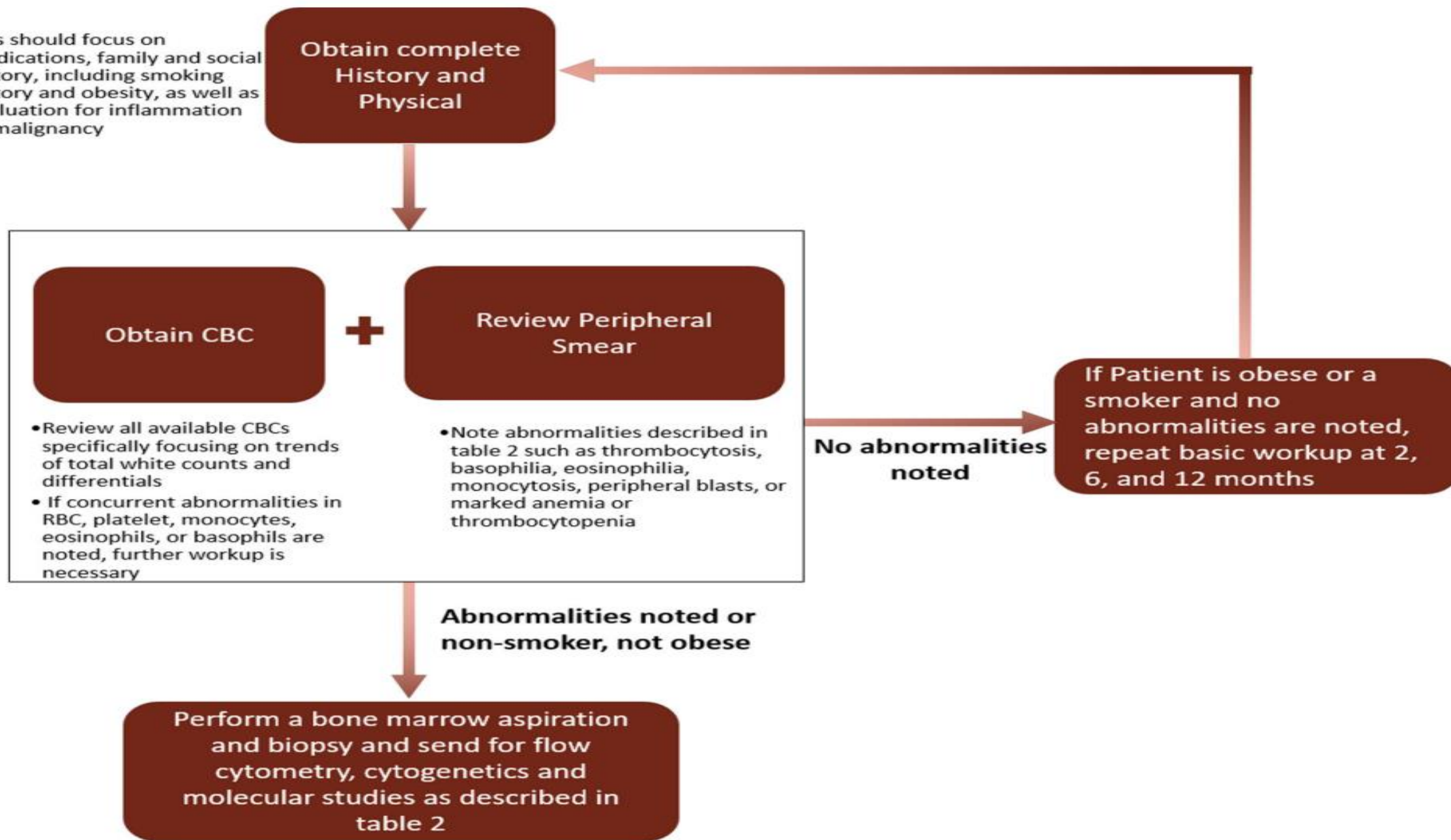


Fig. 1. Algorithm for evaluation of persistent neutrophilia.