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Original Research

Psychological Toxicity in Classical Haematology

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Abstract
Minor blood count irregularities, genetic influences, and low-risk premalignant haematological illnesses can substantially affect patients' psychological and financial well. Individuals with non-malignant illnesses frequently endure heightened anxiety and distress, akin to those with cancer. Referral to a classical haematologist may be difficult due to ambiguities and misconceptions regarding cancer diagnosis. Incidental laboratory abnormalities may necessitate extensive and expensive investigations if not adequately triaged. The absence of consensus guidelines and the limited applicability of contemporary reference ranges exacerbate these issues. While mostly harmless, accidental haematologic results may cause emotional distress, necessitating careful assessment of potential psychological and financial burdens. This article examines the literature about the psychological impact of haematologic disorders, highlights non-pathological factors contributing to fluctuations in laboratory results, and offers strategies to mitigate psychological distress associated with haematologic testing.

Keywords: Psychological, Toxicity, Classical Haematology, Anxiety

Introduction

The human body generates billions of blood cells each day, presenting the haematologist with the complex task of distinguishing benign haematologic changes from genuine disease. A multitude of tests is available to haematologists for quantifying various blood parameters. The complete blood count (CBC) with differential, the most prevalent assay, comprises approximately 30 distinct measures of blood components.

Considering this volume of information, incidental haematological abnormalities are an unavoidable observation. Indeed, approximately 20% of complete blood counts yield at least one "abnormal" result [1]. Normal ranges typically encompass two standard deviations, meaning that by definition, 5% of people naturally fall outside of the "normal" range. Furthermore, the provided normal values do not adequately represent the blood counts distributionacross all populations uniformly [2].Such incidental results may result in a series of additional tests, such as bone marrow biopsies and costly genetic assessments, which can impose considerable financial and psychological burdens if not adequately addressed.

This review seeks to highlight the psychological discomfort a patient may encounter when referred to a haematologist-oncologist for laboratory results that are unlikely to influence their long-term survival. The aforementioned instance of CBC outliers is illustrative; however, this danger also pertains to the diagnosis and treatment of premalignant haematological diseases, low-risk thrombophilia, and various other conditions within the domain of classical haematology. This "psychological toxicity" is still inadequately researched and undervalued in our discipline. It is essential to recognise the significant influence that these referrals exert on patient welfare and the healthcare system as a whole.Shortages of staff and prolonged waiting period for subspeciality referrals might result in excessive and unwarranted referrals or tests, so hindering the scheduling of patients more suitable for haematology referral and causing delays in proper evaluation, diagnosis, and therapy. Moreover, improper testing imposes cost burdens both on individuals and on the healthcare system of the respective country. Haematologists have

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little training in managing the stress associated with diagnostic ambiguity; resources for reducing unnecessary evaluations are scarce, and, regrettably, further assessments are frequently advocated.

We aim to emphasise this problem, which we often face in our clinical work, and provide strategies to mitigate the psychological toxicities that may impede haematology care. This overview presents common haematologic anomalies that have resulted in psychological toxicity in our patients, albeit it is not exhaustive. We examine pertinent literature regarding the emotional detriments of each disorder and seek to pinpoint unresolved enquiries to stimulate further research on the ideal care of these disorders, thereby reducing unneeded evaluations, expenses, and psychological pain for our patients [3-7].

Mild Variations InComplete Blood Count

(1) Mild leukopenia or neutropenia

Although severe type of neutropenia (Absolute Neutrophil Count<500) presents considerable infectious dangers, isolated mild leukopenia or neutropenia (Absolute Neutrophil Count> 1000) in an individual, especially if chronic, should not invariably raise alarm.Numerous authors have advocated for the recognition that established reference ranges in various countries do not accurately reflect the total population [8]. The financial and psychological costs associated with the evaluation of mild neutropenia are inadequately characterised, and there is less evidence regarding the frequency of unnecessary workups and haematology referrals for people with an absolute neutrophil count between 1000 and 1500.Future research and intervention are expected to alleviate considerable psychological harm in this context.

(2)Mild leukocytosis or neutrophilia

Conversely, the expertise of haematologists is frequently requested in cases of moderate neutrophil-predominant leukocytosis lacking a discernible aetiology. The probability of a haematologic malignancy manifesting with isolated neutrophilia is modest, despite its evident association with specific drugs, obesity, systemic infection, smoking, or inflammation. This referral might be particularly alarming for individuals who believe or have been informed by their referring clinician that they may have leukaemia. A brief paper detailing individuals with leukocytosis of indeterminate origin indicated no long-term effects following a 20-year follow-up period [9]. To our knowledge, no studies exist that describe the psychological impact of this minor aberration.

(3)Slight differential irregularities

With the exception of circulatinglymphoid or myeloid blasts, few minor differential abnormalities require urgent attention. A particularly perplexing haematology referral involves aberrant cellular percentages accompanied by normal absolute cell counts; specifically, the percentage of lymphocytes is raised while the absolute count remains normal. This result is infrequently clinically significant if the white blood cell count (WBC) is normal. Relative cell count percentages, typically included in a CBC with differential, are generally inconsequential if the absolute cell counts are in the normal range, leading to additionalfinancial, psychologicaland temporal burdens due to unwarranted referrals.

Although several WBC differential abnormalities exist, solitary eosinophilia is a notably frequent reason for haematology referrals in our experience. Nevertheless, limited information is available regarding the therapy of moderate isolated eosinophilia. In asymptomatic patients accompanied by an inexplicable absolute eosinophil level below 1500, monitoring may be appropriate.

Although the natural history of moderate asymptomatic eosinophilia is inadequately characterised, Chen et al. investigated the clinical implications of hypereosinophilia of uncertain significance (HEUS), characterised by an absolute eosinophil count exceeding 1500 without indications of end organ damage. Among the 36 participants with inexplicable absolute eosinophil count of more than 1500, 8 (22%) were without any symptoms at the time of examination, and all individuals exhibited no laboratory or clinicalsigns of end organ damage over a minimum follow-up period of 5 years [10]. Additional research is required to ascertain the long-term durability and clinical significance of moderate eosinophilia.

(4)Mild thrombocytopenia

The typical platelet level varies from 150,000 to 450,000/μL. Mild thrombocytopenia, characterised by a platelet count ranging from 100,000 to 150,000/μL, may represent a temporary, normal change in numerous individuals. After excluding non-hematologic explanations for low platelet counts, such as infection, hidden liver illness, or drugs, most asymptomatic persons with isolated moderate thrombocytopenia will not experience any related symptoms. A platelet count of less than $100 \times 10^3/\mu L$ is typically regarded as a clinically important threshold necessitating further evaluation in an individual who is stable and asymptomatic in an outpatient context, whereas mild thrombocytopenia (platelets $100–150 \times 10^3/\mu L$) which is stable may be monitored.

A research by Stasi et al. assessed the natural history of moderate thrombocytopenia in 191 people without any symptoms and with platelet level ranging from 100 to $150 \times 10^3/\mu L$ over a median duration of 64 months [11].Thrombocytopenia resolved spontaneously in 64% of instances, with a ten year risk of developing immune thrombocytopenia (ITP), characterised by a persistent platelet count of less than $100 \times 10^3/\mu L$ for the study's purposes. Among people with chronic platelet counts below $150 \times 10^3/\mu L$ after

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five years, 88% had no symptoms. Furthermore, there exists a 12.0% probability of having an autoimmune disorder, with 85% of such disorders manifesting in females.

(5)Mild thrombocytosis

Thrombocytosis, often known as thrombocythemia, is defined as a platelet count over 450 x $10^3/\mu L$ [12]. It is generally categorised into two classifications: primary and secondary. Primary denotes disease entities, such as myeloproliferative neoplasms, resulting from mutations in genes that govern thrombopoiesis. This contrasts with secondary thrombocytosis, or reactive thrombocytosis, which is a benign condition responsible for 80%–90% of increased platelet cases [13]. A variety of factors can lead to transitory secondary thrombocytosis, including physical effort , recovery from thrombocytopenia ,acute infection or inflammation or stress. Chronic causes of high platelet counts may be associated with disorders such as chronic inflammatory or viral diseases, iron shortage, asplenia, or medication responses.

Platelet counts vary depending on age, sex, and ethnicity, according to a cross-sectional study that included 12,142 participants from the Third National Health and Nutritional Examination Survey [14]. For instance, elderly males and females, irrespective of ethnicity, exhibited lesser platelet counts than younger individuals, whereas non-Hispanic blacks demonstrated a greater average platelet count than Caucasians. Upon adjusting for iron insufficiency, women exhibited elevated platelet counts compared to men. Age can significantly influence platelet counts, with adults exhibiting a 35% decrease in platelet count relative to adolescents or neonates [15].

Common Premalignant Haematological Disorders

Numerous haematologic disorders are classified as "premalignant." These precancerous diagnoses are prevalent among elderly adults, with consistently modest annual rates of development to a malignant blood condition.

(1)Monoclonal gammopathy of undetermined significance

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant, clinically asymptomatic clonal plasma cell disorder characterised by a monoclonal protein level below 3 g/dL and without end-organ damage, such as hypercalcemia, anaemia, renal insufficiencyand lytic bone lesions, which are indicative of multiple myeloma (MM). Monoclonal gammopathy of undetermined significance (MGUS) is frequently identified inadvertently using serum protein electrophoresis when assessing other prevalent conditions, including neuropathy,chronic renal disease, dermatological rashes,vasculitis and electrolyte imbalances such as hypercalcemia. It is a premalignant condition with a minimal probability of development, estimated at around 2% over a 20-year span [16]. The identification of a MGUS may necessitate additional diagnostic assessments, including a CBC to analyse haemoglobin, a basic metabolic panel to assess creatinine and calcium levels, immunofixation,serum free light chains, bone marrow biopsy , skeletal imaging such as PET/CT and 24-hour urine protein electrophoresis. After a MGUSdiagnosis, subjects often receive a re-evaluation following a six-month period, accompanied by expedited laboratory evaluations, and may undergo additional assessments in subsequent years based on their risk status.

Universal screening for MGUS in individuals who are asymptomatic is not advised for multiple reasons. The financial implications associated with MGUS are substantial.Secondly, there are considerable potential psychological detriments linked to the diagnosis and continuous monitoring. The decision to conduct extensive diagnostic tests for plasma cell cancers in persons who are asymptomaticshould be judiciously evaluated, including both financial and psychological burdens. Numerous studies have examined the psychological effects of MGUS testing on individuals [17].

(2)Low count monoclonal B lymphocytosis

Monoclonal B cell lymphocytosis (MBL) is characterised by a clonal B cell population identified in the peripheral blood, typically exhibiting the immunophenotype of chronic lymphocytic leukaemia (CLL) having less than 5 x 10^9/L B cells and not having clinical manifestations of a lymphoproliferative illness [18]. Low count MBL is characterised by a clonal lymphocyte count of less than 0.5 × 10^9/L, with an incidence rate of 5% to 12% in people over 40 years and 20% in those over 60 years [19]. The annual probability of MBL advancing to CLL requiring management is roughly 1%.An observational investigation carried out by Fazi et al. examined 138 patients exhibiting low MBL counts in Northern Italy over a median follow-up period of 34 months. The study found that 90% of the participants maintained stable clonal B cell populations, with no instances of advancement to chronic lymphocytic reported[20]. Moreover, there was no disparity in life expectancy between these people and the general public. It is crucial to contemplate the possible psychological detriments associated with screening for conditions like MBL in people who are asymptomatic, which may instead be regarded as a chronic laboratory anomaly that is improbable to advance .

(3)Clonal haematopoiesis of indeterminate potential

Clonal haematopoiesis of indeterminate potential (CHIP) is a premalignant disease, as defined by the World Health Organisation, characterised by the

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existence of a clonal blood cell population exhibiting a somatic mutation in leukemia-associated driver genes having a variant allele frequency of ≥2%, in the absence of cytopenias [21]. Mutations in malignancydriver genes, including DNMT3A , TET2 and ASXL1account for roughly 90% of somatic mutations in clonal haematopoiesis. Risk factors encompassmale gender, age, tobacco smoking and inflammation.Clonal Haematopoiesis of Indeterminate Potential (CHIP) is frequently observed in individuals over the age of 50, with the annual progression rate to malignancy presently estimated at 0.5% to 1%. Assessing the clinical importance of a precancerous illness like CHIP may result in unnecessary overdiagnosis and testing, inducing stress for patients as well as the healthcare practitioners. Due to the absence of recognised pharmacological measures that can modify the natural progression of CHIP, current guidelines do not endorse additional surveillance in asymptomatic people [22].

Low Risk Thrombophilia

Inherited thrombophilia consists of various prevalent genetic risk factors that can elevate the likelihood of thromboembolism development. Factor V Leiden (FVL) is a prevalent genetic thrombophilic disorder caused by the replacement of arginine for glutamine at amino acid position 506. This point mutation induces a conformational alteration in Factor V, resulting in reduced inactivation due to resistance to activated protein C. Prothrombin G20210A is a prevalent inherited thrombophilia caused by a point mutation, wherein guanine is substituted for adenine, leading to enhanced prothrombin mRNA stability. Thrombophilia may also arise from deficits in anticoagulant proteins, including antithrombin, protein C, and protein S. The incidence of hereditary thrombophilia may differ between ethnic groups. In some populations, low-risk thrombophilia is frequently observed.

Routine screening for hereditary thrombophilia in the general population is not advised for various reasons. Thrombophilia is infrequently encountered, with a frequency of 1%–2% for Prothrombin G20210A, antithrombin, protein S and protein C mutation, and 2%–5% for Factor V Leiden (FVL). Secondly, among the impacted carriers, inherited thrombophilia exhibits poor penetrance regarding the manifestation of symptoms such as venous thromboembolism (VTE). A research assessing 470 asymptomatic carriers of the FVL mutation, found through screening of first-degree relatives with a history of VTE with symptoms was conducted during which 9 VTE occurrences were recorded. The annual incidence of spontaneous VTE was 0.26%. The incidence of VTE was 3.5% per surgical, traumatic, or immobilisation episode. None of the 17 full-term gestations in which low-molecular-weight heparin was given as prophylaxis experienced complications from venous thromboembolism The annual frequency of thrombosis was 1.8% among oral contraceptive users and 2.9% among hormone replacement therapy recipients [23].This study indicates that low-risk thrombophilia may not provide a clinically relevant risk of incident venous thromboembolism ,highlighting the necessity for doctors to conduct testing only if it would affect subsequent therapeutic care.

Numerous research have assessed the psychological effects of hereditary thrombophilia screening in asymptomatic patients [24-26].Various researches indicate that screening for hereditary thrombophilia can have varying psychological effects. The decision to do thrombophilia testing in asymptomatic persons should be made with careful deliberation. Individuals with a familial predisposition to thrombophilia and those contemplating medications that may elevate risk of thrombosis, such as hormone replacement therapy or oral contraceptives may find thrombophilia testing results advantageous for informed medical decision-making.

Strategies to Alleviate Psychological Toxicity

Research examining the psychological effects of benign haematologic disorders has pinpointed the haematology referral process as a potential area for change. An increased emphasis on medical education in haematology may alleviate concern for both patients and healthcare practitionerswhen analysing the findings and may reduce needless haematologic evaluations. A clear elucidation of the relationship and differentiation between the departments of haematology and oncology can effectively mitigate any misconceptions concerning a diagnosisof malignancy. Furthermore, an increased focus on recognising and addressing the psychological stressors linked to benign haematologic illnesses in the training of haematology professionals may enhance patient care. The following delineates the areas of intervention:

(1)Minimise superfluous referrals and evaluations before engaging with haematology.

The incorporation and enhancement of haematology education within medical training possess the capacity to enhance healthcare providers' interpretation of prevalent haematologic abnormalities, thereby potentially mitigating unnecessary referrals and diagnostic evaluations. This process can be enhanced by more precisely delineating the laboratory and clinical findings that should prompt a referral to haematology and subsequent evaluation. Instruction on optimal methodologies in domains such as the interpretation of routinely ordered haematologic tests, the assessment of blood count anomalies relative to established reference ranges, and the relevance of additional diagnostic investigations may aid healthcare practitioners in more effectively distinguishing idiopathic haematologic variations from clinically significant diseases. This also prompts an inquiry into whether laboratory examinations ought

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to provide all CBC results, regardless of clinical relevance. Streamlining laboratory testing to focus on essential components may enhance understanding for both patients and providers, while simultaneously minimising superfluous referrals.

(2)Recognise and alleviate discomfort during the initial interaction with haematology

The process of referring patients to a subspecialist can be intimidating and anxiety-inducing, especially when the recommendation pertains to the evaluation of an unclear abnormal laboratory result. The majority of non-malignant haematologists operate within extensive comprehensive cancer centres that exhibit robust interdepartmental connectivity between haematology and oncology. Consequently, the terms “oncology” or “cancer” frequently appear in reference letters, addresses, and the academic titles of haematologists. Patient misunderstandings over benign referrals seen as probable cancer diagnoses can result in unnecessary worry and concern. We recommend the subsequent steps to mitigate this concern for individuals:

(a) Restrict the application of the word “oncology” during interactions with benign haematology patients.

(b) Implement patient navigation to establish expectations of patient. A discussion with the patient coordinator during the referral process can mitigate patient apprehensions by clearly stating that the referral is not for cancer assessment.

(c) Evaluate the increased implementation of electronic "e" consultations. This type of consultation helps mitigate patient distress, along with psychological and financial detriments, by avoiding unneeded referrals and procedures that may incur exorbitant expenditures.

(d)Educate referring providers to alleviate physician apprehension with modest haematologic abnormalities. Electronic consultation and telephonic correspondence serve as valuable resources for physicians to communicate directly, potentially reducing the financial burden of unnecessary testing and appointments while alleviating the transfer of anxiety related to diagnostic uncertainty from providers to patients.

(3)Alleviate anxiety during the haematology appointment

Despite the implementation of methods to alleviate anxiety before haematology appointments, patients are still very likely to experience concerns prior to referral. Recognising and resolving concerns of patient at the outset of the session may alleviate anxiety and clarify possible misconceptions. As the healthcare professional, highlighting any concerns may alleviate unacknowledged stress on the patient who may feel too uncomfortable or ashamed to enquire directly. Indeed, the implementation of these educational opportunities has aimed to mitigate patient stress. The effectiveness of communication may be hindered by the "curse of expertise," wherein one individual proficient in a specific domain presumes that others possess the same foundational knowledge. This concept may pertain to physicians who specialise in a narrow field and may not recognise that patients might not comprehend the delivery of medical information and treatments.By minimising jargon, alarmist language, and nonverbal cues of anxiety, and by focussing on delivering medical treatment through active listening to address concerns, physicians can enhance their patient’spsychological safety [26].

(4)Consider enhancing knowledge on psychological toxicity within haematology training

Training programs of haematology and oncology consistently employ methodologies to sensitively communicate challenging news, particularly concerning cancer diagnoses. The emphasis is on recognising psychological distress linked to challenging malignancy diagnoses or clinical deterioration, potentially leading to additional conversations regarding future medical treatment. However, there is insufficient emphasis on recognising and addressing the emotional detriment experienced by individuals with benign haematologic conditions, which can also impose a psychological burden. Incorporating formal instruction on psychological toxicity into haematology training will enhance healthcare practitioners ability to deliver enhanced and empathetic treatment for their patients.

Conclusion

In conclusion, we emphasise a range of moderate haematologic abnormalities and pertinent studies assessing the natural history of these disorders, many of which areindolent and benign, potentially leading to superfluous diagnostic evaluations and haematology referrals. Considering the cumulative psychological, physical, and financial repercussions of improper referral and testing on patients and the healthcare system, it is advisable for physicians to make judicious and intentional decisions concerning the assessment of moderate blood cell dyscrasias. Implementing solutions, such as integrating electronic consultations and enhancing communication between referring physicians and specialists, can mitigate these effects. Interventions, such as standardising the term “classical haematology,” can diminish referrals which are unnecessary, enhance patient awareness of conditions which arebenignduring the haematology referral process, and improve education for training physicians, thereby alleviating the psychological impacts of benign haematologic disorders.

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