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Multifactorial thrombocytosis directing the diagnostic process - extreme thrombocytosis unveiling pheochromocytoma: case report

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ABSTRACT

Thrombocytosis is a common incidental finding observed in both symptomatic and asymptomatic patients. It can pose a significant diagnostic challenge. Reaching an accurate diagnosis is crucial, as treatment strategies differ considerably. Moreover, it may uncover severe underlying condition. In this report, we describe a clinical case of a patient with extreme thrombocytosis, that ultimately reveled an underlying pheochromocytoma.

Keywords: thrombocytosis, pheochromocytoma, adrenal incidentaloma

1. INTRODUCTION

Thrombocytosis is widely defined as the platelet count exceeding 450,000/μL. Its classification depends primarily on the origin and secondarily on total platelet count (Jeon, 2022). The primary thrombocytosis is typically linked to myeloproliferative disorders, whereas secondary (reactive) thrombocytosis is commonly caused by conditions such as infection, inflammation, tissue damage, medications, iron deficiency, or malignancy (Rokkam et al., 2025). Depending on the total platelet count, thrombocytosis may suggest the underlying cause (Bailey et al., 2017).

Mild thrombocytosis defined as platelet count between 450,000 and 700,000/μL, is often observed in reactive conditions such as infections or inflammation. Moderate thrombocytosis, ranging from 700,000 and 900,000/μL, is typically associated with more severe inflammation or iron deficiency. Platelet counts exceeding 900,000/μL should always be suspicious of more significant conditions, such as myeloproliferative disorders or malignancies (Bailey et al., 2017; Jeon, 2022). The platelet count above 900,000/μL is considered severe. Platelet count exceeding 1,000,000/μL, a condition known as extreme thrombocytosis, is rare, poses a serious risk of thrombotic complications, and requires active investigation into underlying

pathologies, including malignancies. Thrombocytosis, especially extreme, may be the first manifestation of underlying malignancy and is considered a paraneoplastic syndrome (Bailey et al., 2017; Jeon, 2022; Rokkam et al., 2025). Paraneoplastic thrombocytosis has been associated with a variety of cancers, including lung, hepatocellular and ovarian cancers (Abbas et al., 2019; Bailey et al., 2017; Chen et al., 2012). The simultaneous occurrence of extreme thrombocytosis and pheochromocytoma – itself a rare neuroendocrine tumor arising from the adrenal medulla – is highly unusual. We have found only a few case reports describing the association of severe and extreme thrombocytosis with pheochromocytoma (Bazhenova et al., 2005; Chen et al., 2012; Ciacciarelli et al., 2016; Hakke et al., 2024; Suzuki et al., 1991). Some reports describe vascular thrombosis as a first manifestation of pheochromocytoma (Petrák et al., 2024; Y-Hassan & Falhammar, 2020). Only a few similar cases have been documented in the literature, which highlights the rarity and clinical relevance of our case.

In this case report, we aim to present a rare case of extreme thrombocytosis, unveiling an underlying pheochromocytoma. We aim to emphasize the importance of considering malignancy in the differential diagnosis of extreme thrombocytosis in patients with several other possible causes of thrombocytosis.

2. CASE PRESENTATION

A 46-year-old homeless man was transported to the Emergency Room after an attack of convulsions on the street. The patient did not cooperate, was verbally abusive towards the medical staff, and the history taking was impossible. On admission the patient presented with hyponatremia of 110 mmol/l (Reference Range (RR)): 135-145 mmol/l), low blood alcohol level (0.05%), hypoglycemia (68 mg/dl, RR: 70-99 mg/dl), elevated levels of ALT (65 U/L, RR: 0-34 U/L) and AST (208 U/L, RR 5-34 U/L), high and with increasing tendency NTpro-BNP levels (763.80 pg/ml, follow-up measurement: 3,448 pg/ml, RR: 0-125 pg/ml), high level of C-reactive protein (49 mg/l, RR: 0-10), elevated troponin levels (Troponin I 1,330 pg/mL, RR: 0-15 pg/ml) with the decreasing tendency (follow-up measurements: 1,169 pg/mL, 870 pg/ml, 910 pg/mL, 64 pg/mL). The complete blood count (CBC) revealed normocytic anemia, with a hemoglobin level of 10 g/dL (RR: 13.5-18).

On the physical exam, the patient presented extreme neglect with multiple recent and old wounds. However, he did not present any pain symptoms. The patient had normal vesicular breath sounds bilaterally and no pathological murmurs over the heart, with a blood pressure of 130/85 mmHg, and blood oxygen saturation of 95%. Computed tomography (CT) of the head did not reveal any abnormalities.

Intravenous sodium, glucose and fluids were administered, and after performing an electrocardiogram (ECG) (presenting inverted T waves in leads V2-V6, q waves in II, III, aVF, V4-V6) and transthoracic echocardiography (TTE) (presenting segmental wall motion abnormalities, reduced ejection fraction not precisely measured due to the lack of cooperation) suggesting ischemic heart disease, a decision was made to initiate treatment with acetylsalicylic acid, low-molecular heparin and statin. The decision not to perform coronary angiography was made based on the clinical presentation: TTE findings did not correspond with the troponin levels, suggesting that the acute ischemic event had occurred more than 48 hours prior. A similar conclusion was drawn from the evolution of the ECG changes. Additionally, due to low hemoglobin levels and a high likelihood of intestinal bleeding, the decision was made not to pursue full medical treatment for the acute ischemic event.

In the days following admission, history-taking revealed that the patient had experienced a week-long chest pain six months prior to the current admission. Clinically, the patient's overall condition improved. A few days after admission, the patient began physical rehabilitation and, within a few more days, was able to walk—initially with assistance and later independently.

Gastroscopy was performed to investigate the source of bleeding that could explain patient's low hemoglobin levels. The examination revealed a Forrest IIB peptic ulcer (fresh bleeding site in the stomach, partially covered with fibrin). The previously initiated proton pump inhibitor (PPI) therapy was continued. Due to the persistence of cough, a chest radiograph was performed, which did not reveal any abnormalities.

A CBC was performed during hospitalization to monitor hemoglobin levels. It showed a progressive increase in platelet count, from 491,000/μL on admission (RR: 150,000–450,000/μL) to a peak of 1,707,000/μL. The evolution of platelet count during hospitalization is presented in Figure 1. Despite these high levels of platelets, the additional anti-platelet drug was not introduced due to the high risk of bleeding from the gastrointestinal (GI) tract and low hemoglobin levels. This progressive elevation raised suspicion of thrombocytosis secondary to a neoplastic process and has directed the diagnostic and therapeutic pathway.

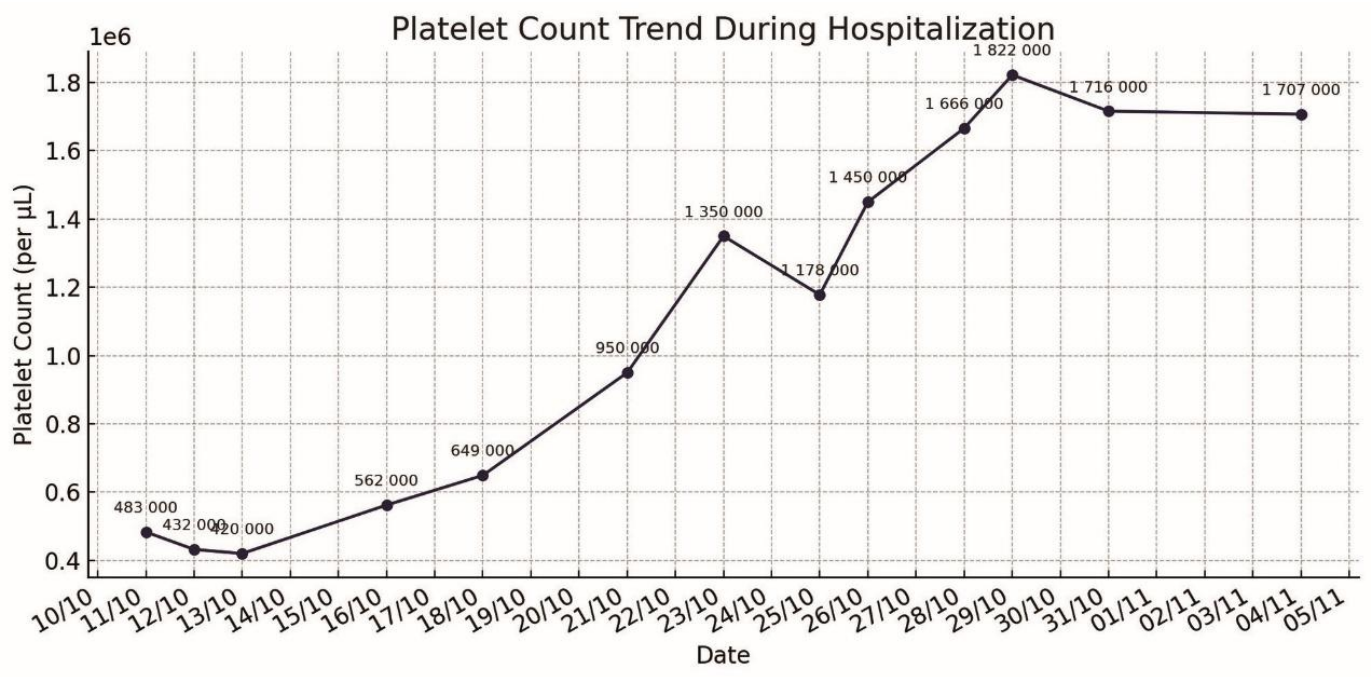

Figure 1. Trend of platelet count (per µL) during hospitalization. A progressive increase was observed, reaching a maximum of 1,822,000/µL.

To assess the abdominopelvic cavity for potential additional bleeding sites and the cause of thrombocytosis, abdominal ultrasonography was performed. It has revealed a suspicious hypoechoic focal mass in the right adrenal gland, measuring 51 × 52 mm. Enhanced CT performed for further evaluation presented a mass in the right adrenal gland measuring 50 × 36 × 42 mm with central calcification and the density of 70 Hounsfield Unit (HU) in the arterial phase, 80 HU on portal venous phase and 56 HU on delayed phase with absolute washout of 67% and relative washout of 30%. These results have confirmed the suspicious character of a mass. CT imaging findings are presented in two figures: Figure 2 shows a coronal plane image acquired in the portal venous phase, while Figure 3 presents an axial plane image obtained during the arterial phase.

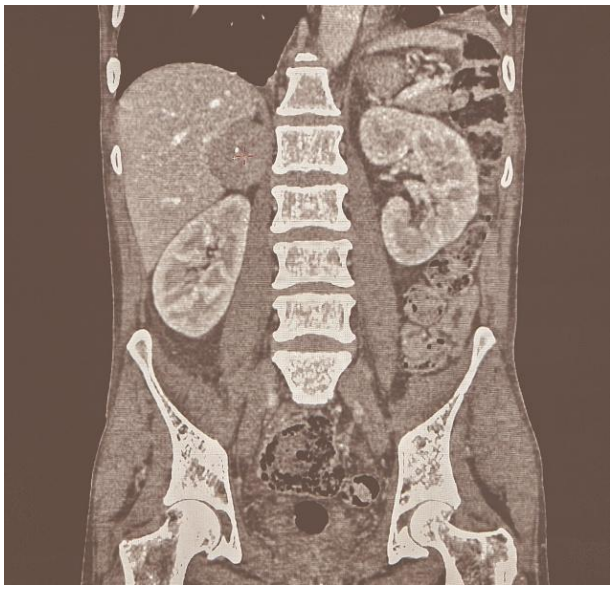

Figure 2. Abdominal CT in the coronal plane, portal venous phase. A hypodense mass in the right adrenal gland with central calcification is visible.

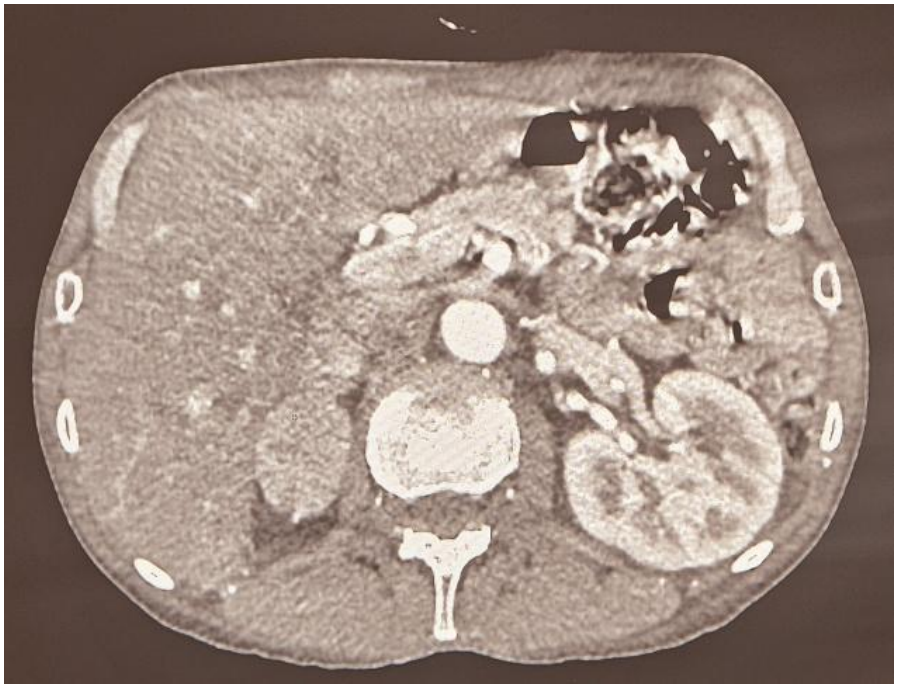

Figure 3. Abdominal CT in the axial plane, arterial phase. The same lesion is visualized in cross-section.

Following consultation with a multidisciplinary team including specialists in internal medicine, urology, and radiology, a decision was made to surgically remove the mass. Before the treatment, it was necessary to exclude the tumor's hormonal activity. In case of catecholamine-producing lesion, initiate sequential treatment with single alpha-blocker therapy with the addition of beta-blockers after 10-14 days. In the meantime, 24-hour Holter monitoring of ECG and blood pressure was carried out. Additionally, history-taking was extended to cover the symptoms characteristic of any syndrome associated with the hormonal activity of the adrenal glands.

The results of 24-hour monitoring were not conclusive, with a mean blood pressure of 149/98 mmHg, a mean daytime blood pressure of 145/95 mmHg, one episode of blood pressure of 198/117 mmHg, and one episode of systolic blood pressure over 200 mmHg; a mean nocturnal blood pressure of 156/103 mmHg, with maximal blood pressure during the night of 169/145 mmHg.

The 24-hour ECG monitoring did not reveal any significant abnormalities. The patient-maintained sinus rhythm, with an average heart rate of 83 bpm, maximal HR of 114 bpm without any additional beats, and pauses of duration over 2000 milliseconds. The maximum RR interval was 1380 milliseconds.

The patient denied the presence of palpitations, cold sweats, pallor, or other symptoms that could suggest pheochromocytoma. The history-taking and laboratory findings were not suggestive of Cushing syndrome either. During the waiting period for the results of cortisol and metanephrines in a 24-hour urine collection, the patient, in a state of significant clinical improvement, was discharged to the temporary place of residence in the Sisters' Congregation.

The results obtained a week after the discharge revealed low cortisol levels excluding Cushing syndrome, and unexpectedly very high methoxy-catecholamines in a 24-hour urine sample with the level of metanephrine 535.65 mcg/24h (RR: 74-297 mcg/24h), normetanephrine 4,287 mcg/24h (RR: 105-354 mcg/24h), 3-metoksytyramin 664.58 mcg/24h (RR: 94-400 mcg/24h). The adrenal gland mass was diagnosed as a pheochromocytoma.

Following the determination of the mass's hormonal status, an adequate preoperative approach was established. Efforts were made to contact the patient to proceed with the treatment. However, contact with the facility to which the patients had been discharged revealed that he had left without any notice and had not provided any means of contact.

3. DISCUSSION

Thrombocytosis: causes and differential diagnosis

Thrombocytosis, commonly defined as a blood platelet level exceeding 450,000/μL, can pose a real diagnostic dilemma, as it can result from a wide range of underlying conditions (Almanaseer et al., 2024; Rokkam et al., 2025; Schafer, 2004). Thrombocytosis is typically

divided into primary (clonal) and secondary (reactive) forms, depending on the underlaying cause (Schafer, 2004; Vannucchi & Barbui, 2007). Sometimes, a third category- familial thrombocytosis- is also distinguished (Schafer, 2001). The distribution of thrombocytosis types is uneven, with secondary thrombocytosis being the most common (observed in 85-90% of patients with elevated patelet counts), while familial thrombocytosis remains extremely rare (Buss et al., 1994; Edahiro et al., 2022; Rokkam et al., 2025). Despite the novel developments and discoveries in the field of genetic causes of primary thrombocytosis, in clinical practice, the diagnosis remains that of exclusion, with further confirmations based on genetic and molecular tests being a highly specialized field beyond the scope of this work (Tefferi & Pardanani, 2019). The causes of secondary (reactive) thrombocytosis are summarized in Table 1.

Table 1. Causes of secondary (reactive) thrombocytosis.

Condition
Acute blood loss
Iron deficiency
Postsplenectomy
Recovery from thrombocytopenia ('rebound')
Malignancies
Chronic inflammatory and infectious diseases (e.g., inflammatory bowel disease, connective tissue disorders, temporal arteritis, tuberculosis, chronic pneumonitis)
Acute inflammatory and infectious diseases
Response to exercise
Response to drugs (e.g., vincristine, epinephrine, all-trans-retinoic acid, cytokines, growth factors)
Haemolytic anemia

The diagnostic process can be complicated, as numerous underlying conditions (Table 1) may result in thrombocytosis. Since management differs between these groups, and in cases of secondary causes, it is primarily focused on addressing the underlying condition, thorough history-taking is essential. Additionally, an optimal diagnostic pathway can help avoid over investigation, unnecessary laboratory and molecular testing, and shorten the time between diagnosis and appropriate treatment. This leads to faster resolution, improved outcomes, and reduced overall healthcare costs. The process should begin with detailed history-taking, which may help identify patients with symptoms characteristic of secondary causes (Table 1). Both thromboembolic and hemorrhagic events are commonly associated with primary thrombocytosis, as this condition is frequently linked to altered platelet morphology and function (Rokkam et al., 2025; Vannucchi & Barbui, 2007). However, such events may also occur in secondary thrombocytosis, particularly in patients with underlying malignancy or when platelet counts are significantly elevated (Vannucchi & Barbui, 2007). Atypical platelet morphology (seen in the blood smear) and spleen enlargement are indicative of primary thrombocytosis (Pedersen et al., 2018; Rokkam et al., 2025). Another differential factor that could help in the diagnostic pathway is the platelet blood count. Based on limited data, patients with secondary thrombocytosis usually exhibit lower platelet counts, with over 90% falling into the category of mild thrombocytosis. A platelet count exceeding $1{,}000\times10^9$ /L in patients with secondary thrombocytosis is considered extremely rare. In contrast, in patients with primary thrombocytosis, platelet counts are usually higher, with extreme thrombocytosis in around 30% of patients. Other indications are high lactate dehydrogenase (LDH) and potassium levels, which are suggestive of primary thrombocytosis (Edahiro et al., 2022). In the case of the patient described in our case, there were multiple potential causes of secondary thrombocytosis (inflammation, anemia), but at the same time, the platelet count and recent probable thromboembolic event were suggestive of primary thrombocytosis. LDH levels were not monitored, while potassium levels were elevated to a degree necessitating insulin-glucose administration. However, the elevation was attributed to the initiation of hypotensive therapy.

While considering the secondary causes, it is crucial to exclude malignancy. The pathophysiology of malignancy-associated thrombocytosis involves the release of pro-inflammatory cytokines and growth factors, including interleukin 6 (IL-6), thrombopoietin (TPO), growth-regulated oncogene (GRO), transforming growth factor beta (TGF-beta) or granulocyte macrophage colony-stimulating factor (GM-CSF) (Harano et al., 2017). The most common neoplasms associated with thrombocytosis are lung and colorectal cancers, with other types of neoplasms showing weaker association (Bailey et al., 2017; Edahiro et al., 2022). In terms of pheochromocytoma, the secretion of catecholamines further contributes to the stimulation of thrombocyte production (Chen et al., 2018). The recognition of

thrombocytosis, particularly in its extreme form, as a potential paraneoplastic marker is essential for facilitating early diagnosis and treatment and thus improving patient outcomes. It also enables appropriate monitoring and management of the clinical consequences of thrombocytosis, including deep vein thrombosis, pulmonary embolism, ischemic stroke, and other less common thromboembolic events.

While inconclusive, the finding of a suspicious mass in our patient's adrenal gland has directed the diagnostic process to consider thrombocytosis as an event secondary to the neoplastic disease. This conclusion led to the decision to address the underlying cause rather than intensify treatment of thrombocytosis itself.

Adrenal masses: characteristic and approach

Adrenal incidentalomas are defined as adrenal tumors measuring 1 cm or more, discovered incidentally on imaging studies performed for reasons unrelated to adrenal glands evaluation (Hu et al., 2024; Janiak et al., 2024). The prevalence of incidentalomas varies between studies and is estimated to be around 5% of radiological studies (Bernardi et al., 2022). Most adrenal tumors are benign, with an estimated malignancy rate from 1.9% and 4.7% (Cawood et al., 2009). Most of them do not present any hormonal activity, with the rate of hormonally active tumors being estimated between 70% to 86% (Hu et al., 2024, Okroj et al., 2023). Despite their typically benign nature, two crucial questions to pose when discovering incidentalomas are: whether the tumor is hormonally active and/or malignant (Cawood et al., 2009; Okroj et al., 2023). All the patients with incidentalomas should undergo additional tests to determine whether the tumor is hormonally active (Hu et al., 2024).

According to the guidelines of the European Society of Endocrinology, all patients should undergo tests to determine whether the tumor produces cortisol, even in the absence of clinical signs of Cushing syndrome, with the 1 mg suppression test of dexamethasone. Testing for primary aldosteronism or steroid profiling should be reserved for the group of patients with symptoms typical of the excess of these particular hormones. Laboratory testing for pheochromocytoma should be reserved for the group of patients with radiological findings that are not typical for a benign mass (Fassnacht et al., 2023; Janiak et al., 2024). Another key consideration in the evaluation of patients with an incidentaloma is the potential malignant character of the mass. A detailed discussion of the radiological criteria used to assess the nature of incidentaloma is beyond the scope of this paper. However, briefly, homogenous masses with the density below 10 HU do not require further evaluation or follow-up, which reflects a significant update in the latest guidelines (Janiak et al., 2024).

Management of patients with adrenal incidentalomas should be individualized, and decision should be made by a multi-disciplinary team including a radiologist, an endocrynologist, and a surgeon. In general, patients with suspected malignancy and/or hormone-producing tumors should be considered for surgical treatment. Biopsy is not recommended in any case (Fassnacht et al., 2023; Janiak et al., 2024). In our patient, contrast-enhanced CT enabled clear classification of the adrenal mass as suspicious for malignancy and therefore qualified for surgical treatment. The patient's unstable social situation was an additional factor supporting the decision, with the high risk of the patient's absence in case of radiological follow-up exams. To the previously ordered free evening cortisol test, a test for fractionated metanephrines in a 24-hour urine sample was added to exclude the presence of a catecholamine-producing neoplasm. Hormonal tests indicated a low likelihood of cortisol-producing adrenal mass, and the unexpectedly high metanephrine levels led to the conclusion that the adrenal gland mass was a pheochromocytoma.

Pheochromocytoma: approach and treatment

Pheochromocytomas are rare catecholamine-producing tumors and account for between 1% and 5% of adrenal incidentalomas (Anagnostis et al., 2009; Janiak et al., 2024). They are frequently associated with genetic diseases, especially when bilateral (Bernardi et al., 2022). Pre-operative preparation (surgical treatment is recommended in all patients) is crucial to avoid potentially life-threatening situations associated with the release of massive quantities of catecholamines during surgery, even in the case of asymptomatic patients, and requires sequential treatment with a single alpha-blocker 10-14 days before the operation and in case of tachyarrythmias or tachycardia addition of beta-blocker(after the installment of alfa-blockage) (Lenders & Eisenhofer, 2017). Unfortunately, in the case of our patient, after the discharge from the hospital and the anticipation of the results of fractionated metanephrines in a 24-hour urine sample and the operation, the patient disappeared from our radar, and all attempts to find him have failed.

4. CONCLUSION

The causes of thrombocytosis require a thorough differential diagnosis, which is essential not only to treat its complications but also to address its origin. This case highlights the complexity of the diagnostic process and the importance of considering malignancy as a

potential underlying cause of thrombocytosis, as well as underlining the challenges of approaching the patient with a difficult socio-economic situation.

Abbreviation	Full Term
ECG	Electrocardiogram
TTE	Transthoracic Echocardiography
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
NT-proBNP	N-terminal pro B-type Natriuretic Peptide
CRP	C-reactive Protein
CBC	Complete Blood Count
GI	Gastrointestinal
PPI	Proton Pump Inhibitor
CT	Computed Tomography
RR	Reference Range
HR	Heart Rate
HU	Hounsfield Unit

Author's Contributions

Conceptualization, M.K, A.B. and A.Z.; Methodology, M.K., A.B; Software, A.Z.; Validation, A.Z and M.W., and M.B.; Formal Analysis, J.B.K, K.H., S.S.; Investigation, P.K., M.B.; Resources, K.H., M.B.; Data Curation, P.K., K.S., K.H.; Writing – Original Draft Preparation, M.K., A.B., M.L., K.S. and A.Z.; Writing – Review & Editing, M.K., M.W., P.K., K.H., S.S. and J.B.K.; Supervision, A.B., M.K.; Project Administration, A.B., J.B.K., A.Z., M.L., K.S., M.K., K.H, M.B.

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Informed consent

Written & Oral informed consent was obtained from patient included in the study.

Ethical approval

Not applicable.

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Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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