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PANSITOPENIA: CHALLENGES OF APPROACH AND CASE HANDLING IN PERIPHERAL HOSPITALS

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ABSTRACT

Pancytopenia is a hematological condition characterized by a decrease in three blood cell lines: erythrocytes, leukocytes, and platelets. This condition is not an independent disease, but a manifestation of various underlying diseases. Pancytopenia can be caused by impaired blood cell production in the bone marrow or increased destruction of blood cells in the periphery. Precise and prompt identification of the etiology is essential, given that pancytopenia can be life-threatening if not treated properly. This study aims to analyze and identify the causes of pancytopenia in patients at Batang Regency Hospital, as well as provide recommendations for appropriate treatment based on the etiology found. The methods used were clinical observation, laboratory examination, and diagnostic imaging in a 58-year-old patient with the main complaint of weakness and a history of pancytopenia. The examination includes a complete blood count, a smear of peripheral blood, and a clinical evaluation. The results showed that the patient had central type pancytopenia, with a suspected etiology of aplastic anemia or myelodysplastic syndrome. Other differential diagnoses include vitamin B12 deficiency. Although a bone marrow biopsy is necessary to confirm the diagnosis, initial therapy with blood transfusions and nutritional improvements has shown an improvement in the patient's condition. The conclusion of this study is the importance of a thorough evaluation to identify the etiology of pancytopenia. Proper treatment should be based on the underlying cause, which will affect the prognosis and prevent recurrence. A comprehensive approach can improve patients' quality of life and reduce the risk of complications.

KEYWORDS *Pancytopenia, Aplastic Anemia, Myelodysplastic Syndrome, Transfusion*

INTRODUCTION

Pancytopenia is a hematological condition characterized by a decrease in the three blood cell lines. The condition is characterized by hemoglobin values of less than 12 g/dL in women and 13 g/dL in men, platelets less than 150,000 per mL, and leukocytes less than 4000 per ml (or an absolute neutrophil count of less than 1800 per ml). However, this threshold depends on age, gender, race, and various clinical scenarios. Pancytopenia itself is not a disease but a manifestation of another underlying condition. This condition is generally associated with various conditions, whether benign or malignant. Pancytopenia

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can be caused by decreased cell production or increased damage. Anyone with pancytopenia needs a thorough evaluation to identify the underlying etiology (Island, 2021a).

The incidence of pancytopenia is often seen in children and adults in the 3rd and 4th decades. Research shows that the ratio of men and women is 1.4:2.6.[2] While conditions such as multiple myeloma and myelodysplastic syndrome are more common in older patients, acute leukemia and parvovirus B19 infection are more common in younger patients. In North America, the most common etiology is myeloid neoplasms (acute myeloid leukemia, myelodysplasia, non-Hodgkin lymphoma, *hairy cell* leukemia, and precursor B acute lymphoblastic leukemia), followed by aplastic anemia, megaloblastic anemia, and HIV infection (Island, 2021a).

The spread of the etiological causes of pancytopenia often varies by geographic region, age, and gender (Yokus & Gedik, 2016). Geographical, social and cultural influences determine the cause of significant pancytopenia, especially for megaloblastic anemia. For megaloblastic anemia, there is usually no gender dominance. There are seen to be more cases in the Eastern states than in the West, most likely due to the incidence of infections and the drugs used, which lead to higher pancytopenia in developing countries (Nell & Chapanduka, 2022).

The causes of pancytopenia can mostly be grouped into peripheral cell damage disorders, or impaired bone marrow production. However, most conditions tend to exhibit the characteristics of both, as pancytopenia can arise from a variety of different pathophysiological mechanisms (Drakel et al., 2022). The etiology of pancytopenia is broadly divided into central types involving manufacturing/production disturbances or peripheral types involving disturbances of increased damage/destruction. These causes can cause pancytopenia separately or in combination (Island, 2021a).

The etiology of pancytopenia varies. The morbidity and mortality of pancytopenia depend on the variability of etiology, but it is most common due to the effects of anti-cancer therapies such as chemotherapy, *Human Immunodeficiency Virus* (HIV) infection, infiltration or failure of the bone marrow. Drugs, especially antirheumatic agents, phenylbutazone, anticonvulsants such as hidantoin, carbamazepine, cytotoxic drugs (alkylation agents), antibiotics (chloramphenicol, sulfonamides) are drugs that are one of the triggering factors . In the following, pancytopenia is categorized into two causes:

1. Production decline (central type)

Pancytopenia due to decreased production, can be caused by; a deficiency of a nutrient source that causes impaired cell production, infiltration of the bone marrow by malignancy, or hypocellular bone marrow. Pancytopenia can also be caused by bone marrow failure, known as aplastic anemia. Aplastic anemia can be idiopathic/autoimmune, caused by infection (such as parvovirus B-19, hepatitis, *human immunodeficiency virus* (HIV), *cytomegalovirus*, or *Epstein-Barr* virus), due to drug poisoning, or due to chemotherapy agents (methotrexate, dapson, carbimazole, carbamazepine, chloramphenicol). Pancytopenia can also be associated with inadequate intake (as seen in eating disorders and alcoholics) or malabsorption therapy.[1] Disruption of the production of bone marrow can lead to pancytopenia. It is usually accompanied by a low number of reticucytes, which indicates a poor bone marrow response. Nutritional deficiencies such as vitamin B12 deficiency lead to incomplete DNA synthesis, which leads to pancytopenia with megaloblastic anemia, which can be identified by macrocytosis or hypersegmentation neutrophils on blood smears, and the number of reticulocytes is thought to be low. Folate deficiency and drugs that inhibit dihydrofolate reductase such as methotrexate and trimetoprim can also lead to megaloblastic anemia, through the same mechanism. However, isolated macrocytosis should be interpreted with caution, as reticulositosis can lead to false macrocytosis Less common nutritional causes of pancytosis include copper

deficiency or excess zinc and can present with associated neurological deficits (Chew & Kamangar, 2024).

Furthermore, pancytopenia is the result of bone marrow infiltration. Cell production will also be disrupted when the bone marrow is infiltrated by malignancies (lymphoma, leukemia, multiple myeloma) or granulomatose abnormalities. Metastatic tumors can also cause replacement of bone marrow contents which in the later stages of the disease can lead to pancytopenia.[1] Malignancy that infiltrates and replaces normal hematopoietic cell lines, disrupting bone marrow production. Common hematological malignancies that emerge with pancytopenia include acute myeloid leukemia, acute promyelocytic leukemia (APML) and myelodysplastic syndrome. Common blood smear morphologies include macrocytosis, the presence of circulating blast cells with or without Auer stems, or leukoeritroblastic blood smears. The presence of double-lobed granular blast cells on the blood smear indicates APML. In addition, myelofibrosis presents with massive splenomegaly, *tear drop* cells on blood smears and an inability to aspirate the bone marrow. Further investigation by a haematologist including bone marrow aspiration and *a trephine* biopsy is usually necessary, and may reveal hypercellular or hypocellular bone marrow. In suspects of APML, it should be immediately referred to a hematologist for treatment with All-Trans Retinoic Acid (ATRA) and chemotherapy, due to the high risk of DIC.

Aplastic anemia appears with pancytopenia due to the hypocellular bone marrow, with a decrease in the production of all three cell lines. Other differential diagnoses to consider, especially in younger patients, include the causes of bone marrow failure in hereditary diseases, such as *Fanconi anemia*, *Shwachman–Diamond syndrome*, and *congenital dyskeratosis*. The presence of splenomegaly or anisocytosis, or the absence of mild macrocytosis makes the diagnosis of aplastic anemia unlikely. Lymphadenopathy is also uncommon in aplastic anemia, and infection should be considered instead. Aplastic anemia is diagnosed by bone marrow aspiration and *trephine* biopsy. Iatrogenic causes such as alcohol, radiotherapy and drugs can also cause pancytopenia due to bone marrow suppression. Certain infections such as parvovirus B19 and *Human Immunodeficiency Virus* (HIV) can also interfere with bone marrow production, leading to pancytopenia. Genetic conditions such as *Gaucher*'s disease, an autosomal recessive congenital disease that causes glucoserebrosidase deficiency in lysosomes, can also cause pancytopenia through bone marrow infiltration and hypersplenism.

Table 1. Etiology of Central Type Pancytopenia

Decline in Production	**Bone Marrow Infiltration**
Autoimmune disorders (e.g., systemic lupus erythematosus [SLE], rheumatoid arthritis [RA], sarcoidosis)	**Non-violence**
Hemophagocyte lymphocytosis (HLH)	• Myelofibrosis
Aplastic anemia/paroxysmal nocturnal hemoglobinuria	• Infections (e.g., fungal, tuberculosis)
Medicines	• Diseases in storage
• Cytotoxic drugs	**Malignancy**
• Idiosyncratic reactions to drugs	• Acute leukemia
Large granular lymphocyte leukemia	• Chronic leukemia/myeloproliferative neoplasms (MPN)
Nutritional disorders (vitamin B12 and folate deficiency, excessive alcohol consumption, malnutrition)	• Myelodysplastic syndrome (MDS)
Viral infections	• Multiple myeloma

	• Metastatic cancer

2. Increased damage (peripheral type)

Peripheral cell damage in pancytopenia can be associated with many autoimmune conditions (such as systemic lupus erythematosus, rheumatoid arthritis) and spleen sequestration (alcoholic liver cirrhosis, HIV, tuberculosis, malaria). Hypersplenism affects platelets and erythrocytes more than leukocytes. Pancytopenia can occur due to damage of peripheral cells by the reticuloendothelial system, such as the spleen in hypersplenism. Hypersplenism occurs due to splenomegaly and subsequently the sequestration of red blood cells, white blood cells, and platelets in the spleen. It can be caused by secondary portal hypertension due to chronic liver disease (which can be caused by alcohol, hepatitis B, or hepatitis C). Less common causes of hypersplenism include infections (such as malaria, *Epstein-Barr virus* (EBV), cytomegalovirus, schistosomiasis, and leishmaniasis), autoimmune conditions, chronic hemolytic disease, and malignancy. Certain autoimmune conditions such as systemic lupus erythematosus, rheumatoid arthritis, and *Felty* syndrome, as well as sarcoidosis cause pancytopenia, which is caused by hypersplenism or autoimmune damage to cell lines by autoantibodies (Gnanaraj et al., 2018).

Table 2. Etiology of Pancytopenia Peripheral type

Damage Increase
Consumption
• disseminated intravascular coagulation (e.g., associated with sepsis, acute promyelocytic leukemia)
Splenomegaly
• Portal hypertension/cirrhosis
• Infection (e.g., EBV)
• Autoimmune disorders (e.g., SLE, RA/Felty syndrome)
• Myelofibrosis with myeloid metaplasia
• Storage diseases (e.g., Gaucher)
• Malignancy (e.g., lymphoma, MPN)

Table 3. Medications That Cause Pancytopenia

Non-steroidal anti-inflammatory drugs (OAINS)	**Cardiovascular**
Aspirin	Aspirin
Salicylates	Lisinopril
Ibuprofen	Amiodarone
Indomethacin	Nifedipine
Diclofenac	Captopril
Sulindac	Quinidine
Anti-Microbial	Thiazides
Albendazole	Acetazolamide
Cidofovir	Furosemide
Dapsone	**Anti-Gout**
Ganciclovir	Allopurinol
Foscarnet	Colchicine
Sulfonamides	**Anti-Epilepsy**
Quinidine	Carbamazepine
Quinine	Fosphenytoin
Zidovudine	Phenytoin
Rheumatology	Phenobarbital
Leflunomide	Valproate
Methotrexate	Levetiracetam

Sulfasalazine	**Psychiatry**
Penicillamine	Bupropion
Anti-Thyroid	Lithium
Methimazole	Valproate
Propylthiouracil	Carbamazepine

Despite extensive examination, some patients develop unexplained cytopenia, which is classified as idiopathic cytopenia of unknown significance. The etiological causes of pancytopenia vary depending on the patient's age, gender, country, and other conditions. Vitamin B12 deficiency is the most common and treatable cause of pancytopenia (Rehmani et al., 2016). The rest are chronic liver disease, then malignancy, myelodysplastic syndrome, aplastic anemia, rheumatic causative agent and finally endocrine causes. Most etiological causes can be diagnosed by laboratory analysis and radiological imaging, without the need for bone marrow examination.

Table 4. The Most Common Etiology of Pancytopenia According to (Yokus & Gedik, 2016) Based on Gender and Age

Age and Gender	Etiology of Pansitopenia		
Age over 65 years	Chronic Liver Disease	Myelodysplastic syndrome	Malignancy
Age less than 65 years	B12 vit deficiency	Aplastic anemia	Treatment
Age over 65 years and Female	Chronic Liver Disease	Malignancy	Myelodysplastic syndrome
Age over 65 years and Male	Myelodysplastic syndrome	Deficiency of Vit B 12	Malignancy
Age less than 65 years old and Female	Treatment	Rheumatic Diseases	Porta hypertension
Age less than 65 years and Male	B12 vit deficiency	Aplastic Anemia	Malignancy

Table 5. Distribution of various causes of pancytopenia according to a study by (Rao, 2011)

No.	Cause	Percentage
1	Mgaloblastic anemia	74,04%
2	Aplastic anemia	18,26%
3	Subleukemic leukemia	3,85%
4	Malaria	1,93%
5	Multiple myeloma	0,96%
6	Storage disruption	0,96%

Diagnosis can take a long time, depending on the doctor's experience and knowledge, as well as the cause of pancytopenia. Many diseases cause pancytopenia, and the frequency of these diseases varies by country, gender, and age. These causes tend to be less severe. For example, the common cold virus causes temporary pancytopenia, but Aplastic Anemia (AA) and Myelodysplastic Syndrome (MDS) can be fatal. Vitamin B12 deficiency and the cause of infection are common in underdeveloped and developing countries, while the cause of malignancy predominates in developed countries (Tapse, 2017). Based on research by *Vargas-Carreto et al*, on the etiology of pancytopenia in adult populations categorized by continent, the most common causes include megaloblastic anemia due to vitamin B12 deficiency, aplastic anemia, hypersplenism, or malignancies including myelodysplastic syndrome and acute myeloid leukemia. The etiological causes of pancytopenia and their extent can differ in each study from the same and different countries. However, most etiological causes of pancytopenia are associated with non-hematological diseases and are diagnosed by laboratory tests without the need for bone marrow examination.

Pathophysiology

The underlying pathophysiology depends on the cause of pancytopenia. The pathophysiology of aplastic anemia is caused by an autoimmune mediated process mediated by T cell activation, which causes the destruction/damage of hematopoietic stem cells. Bone marrow suppression is also caused by the direct cytotoxic effects of drugs such as methotrexates, anticonvulsants, and chemotherapy agents. Ineffective hematopoiesis is seen in the bone marrow in myelodysplastic syndrome (Island, 2021a).

Sepsis can cause pancytopenia through several mechanisms (bone marrow suppression, hypersplenism, and *disseminated intravascular coagulation* (DIC)), which usually appear in combination. The virus causes pancytopenia through several mechanisms that modulate hematopoietic stem cells. Paroxysmal nocturnal hemoglobinuria is a genetic disease caused by the absence of *glycophosphatidylinositol-related* proteins, such as *CD55* and *CD59*, which prevent complement-mediated cell damage. It involves a mutation of the class A protein *of phosphatidylinositol glycana*.

Diagnosis

1. Anamnesis and Physical Examination

Clinical presentation can vary, with mild asymptomatic pancytopenia to life-threatening emergencies in severe pancytopenia. Symptoms appear due to impaired cell function involved, and include fatigue, infection, and bleeding. However, pancytopenia is often only identified on a blood test because of its non-specific presentation. Patients may show manifestations of one of the declining cell lines. Anemia can appear as shortness of breath, fatigue, and chest pain. Leukopenia manifests as an increase in infection, whereas thrombocytopenia presents with bruising, petekie, and a tendency to bleed. Patients with severe neutropenia may present with severe infection. Patients with underlying liver disease may present with anorexia, nausea, or lethargy. Patients with spleen sequestration may present with upper left quadrant pain. Constitutional symptoms can be seen in patients with an autoimmune disorder or underlying malignancy.

History is very important in the evaluation of pancytopenia. This should include an investigation of symptoms of an autoimmune condition, malignancy, recent infection, medication, chemotherapy, or radiation therapy. A detailed history of nutritional status should be taken. It should be noted that the manifestations of malabsorption may not be visible, and pancytopenia may be the only manifestation. Family history should also be considered for inherited aplastic anemia.

Physical examination may show paleness, petekie, ulcers, and rashes. Signs of underlying liver disease can be seen in patients with cirrhosis. Splenomegaly can be seen in patients with spleen sequestration. Lymphadenopathy can be seen in patients with infections and lymphoma. Attention should be paid to the signs of nutritional deficiencies in patients with eating disorders and alcoholism. The neurological examination is very important because it can show proprioception disorders with a positive Romberg test and ataxia, which indicates a secondary subacute combined degeneration of the spinal cord due to vitamin B12 (cobalamin) deficiency and macciterly anemia. Splenomegaly and hepatomegaly are seen in cases of megaloblastic anemia, followed by subleukemic leukemia and malaria. Bone pain is seen in multiple myelomas. Lymphadenopathy is seen in subleukemic leukemia – a type of lymphoblast.

The most common clinical manifestations in Pancytopenia include fever (86.7%), fatigue (76%), dizziness (64%), weight loss (45.3%), anorexia (37.3%), night sweats (28%), paleness (100%), splenomegaly (48%), hepatomegaly (21.3%), lymphadenopathy (14.7%), and bleeding (38.7%). This disorder is most likely caused by thrombocytopenia-induced clotting disorder that then causes excessive bleeding even after mild trauma.

2. Supporting Examination

The initial examination includes a complete blood count, along with a reticulocyte count. This will help determine whether pancytopenia is secondary to a decrease in production. The average blood cell volume will lead to megaloblastic anemia. Peripheral

blood smears can show abnormal cells such as blast cells, dysplastic leukocytes, and immature cells. These abnormal cells may be related to the condition described in table 6. Diagnoses related to abnormal cells may require further examination:

a. Bone marrow aspiration and biopsy
b. Cytogenetic examination (*In Situ Fluorescence Hybridization* [FISH] or karyotype) of bone marrow or peripheral blood
c. *Flow cytometry* of bone marrow and/or peripheral blood
d. Molecular studies (e.g., mutation analysis, gene expression profiling)
e. The examination should also include vitamin B12 and folate levels, liver chemistry, and lactate dehydrogenase.

Infection screening should be done because pancytopenia can be associated with infections such as HIV, malaria, and tuberculosis. In cases of secondary pancytopenia due to acute viral infection, further examination is not necessary because most recover quickly. Further laboratory examinations may be performed to ensure pancytopenia resolution. Similarly, in severe infections with sepsis, follow-up examination should not be done because pancytopenia is most likely a consequence of sepsis. Termination of infection/sepsis will improve pancytopenia.

Further evaluation for undiagnosed hepatitis and autoimmune conditions or malignancies should be performed if suspected. Serum calcium levels and parathyroid hormone can help patients with negative test results, as there are cases of hyperparathyroidism that causes pancytopenia. A thyroid profile should also be obtained, as hyperthyroidism is associated with pancytopenia.

Aspiration and bone marrow biopsy may be performed if no specific etiology is found to evaluate the status of bone marrow stem cells. Bone marrow aspiration establishes the diagnosis of pancytopenia in 75% of cases. The most common etiology found is hypoplastic bone marrow, followed by megaloblastic anemia and hematological malignancy. Pathological examination of bone marrow biopsy is useful in malignant etiology. This examination may show clonal cell populations, primary/secondary malignant cells, acellular bone marrow, fibroblasts, granulomas due to tuberculosis, sarcoidosis, or fungal infections.(Island, 2021a)

Table 6. Abnormal Cells That May Be Found in Blood Drain[1]

Cell Type	Related Conditions
Circulating blast cells	Acute leukemia, hairy cell leukemia, or other hematological malignancies
Dysplastic leukocytes, including pseudo-Pelger-Huët cells	Myelodysplastic syndrome
Immature myeloid cells, such as promielocytes, myelocytes, and metamyelocytes	Myeloproliferative (MPN) neoplasms, such as primary myelofibrosis
Nucleated red blood cells	Myelofibrosis or other MPNs
Hypersegmentation neutrophils	Folate and/or vitamin B12 deficiency
Cystocytes or other evidence of microangiopathic hemolytic anemia (MAHA)	Disseminated intravascular coagulation / DIC
Appearance of leuchoeritroblastic on blood smears, with RBC Teardrops, nucleated red blood cells, and MAHA	Metastatic cancer or myelofibrosis

Once pancytopenia is confirmed at the initial complete blood count, the initial non-invasive examination should include a reticulocyte count and a smear of blood. The reticulocyte count is a good substitute indicator for bone marrow response, where a low reticulocyte count will lead to bone marrow production disorders, while an increased reticulocyte count will indicate peripheral damage. Blood smears will also provide insight

into cell morphology, and will help to diagnose hematological malignancies or megaloblastic anemia. Early referral to haematology is required for further imaging and bone marrow biopsy if clinically suspicious for hematological malignancies is found. The patient's history should also be reviewed to assess the possible etiology of the disease. This should include an assessment of related symptoms such as fatigue, jaundice, easy bruising or recurrent bleeding, recurrent infections, constitutional symptoms of fever over 38°C, heavy night sweats, or accidental weight loss of more than 10% in the past 6 months. Past medical history including exposure to drugs or toxins should be questioned, to assess the cause of alcohol or iatrogenic pancytopenia. A travel history can raise suspicions of a tropical infection that causes hypersplenism. A family history with a genetic condition should also be checked. A full-body examination, including unusual bruises, petekie or purpura, and examination of the lymph nodes and abdomen for hepatomegaly or splenomegaly should be performed. Useful signs for assessing splenomegaly include dimming of percussion in *Traube*'s room, and the onset of *Castell's sign*. Ultrasound should be considered to determine the size of the spleen, which should not be larger than 13 cm. The presence of a massive spleen of more than 20 cm should raise suspicions of chronic myeloid leukemia, myelofibrosis, malaria, schistosomiasis, leishmaniasis or Gaucher's disease. Splenomegaly is unlikely to occur in aplastic anemia, megaloblastic anemia, and most cases of myelodysplasia. Based on clinical findings, further examination should focus on explaining the etiology of common diseases, including liver disease (including liver function tests and blood clotting tests), viruses (including hepatitis B, hepatitis C, EBV, cytomegalovirus, parvovirus B19 and HIV) and parasitic infections (including malaria, schistosomiasis and leishmaniasis), hemolytic examinations for cell damage (including haptoglobin and direct antiglobulin testing), autoimmune examinations for rheumatic diseases (including erythrocyte sedimentation rate and autoantibody testing), and nutrient deficiencies (including hematinic, copper serum and seruloplasmin).

Treatment/Handling

Treatment is based on the underlying etiology of pancytopenia. Nutritional deficiencies must be corrected. Any medication that triggers pancytopenia (methotrexate, linezolid, or anticonvulsant) should be discontinued immediately. Treatment for infections such as HIV or tuberculosis should be started immediately. If an autoimmune condition or malignancy is diagnosed, it should be treated. Secondary aplastic anemia due to viral infections such as parvovirus is temporary and symptomatic treatment is sufficient. Treatment options for patients with severe aplastic anemia may include hematopoietic stem cell transplantation and immunosuppression. Hematology referrals should be sought for patients with severe aplastic anemia.

Supportive care for patients includes red blood cell transfusions for anemia to alleviate symptoms and perfusion of vital structures. Platelet transfusions are indicated for thrombocytopenia of less than 10,000 per mL to prevent spontaneous intracranial bleeding. Broad-spectrum antibiotic therapy should be started immediately for patients with neutropenia fever or severe neutropenia with an absolute neutrophil count of less than 500 per ml due to the risk of death from sepsis.

Management of pancytopenia is usually directed at the underlying cause, with supportive additions such as antibiotics for severe neutropenia and limited blood transfusion strategies to maintain hemoglobin above 7 g/dL. In unhealthy patients where common causes have been ruled out, clinical gestalt of less common causes should be considered. Specific investigations include flow cytometry for PNH, and aspartate aminotransferase levels, ferritin, triglycerides, and fibrinogen for H-score calculations for HLH. The involvement of a haematologist and/or rheumatologist may be required for further management.

Pancytopenia can be grouped into either a cause of peripheral damage or a cause of impaired bone marrow production, although in reality most conditions arise with a combination of both. Taking into account such an extensive list of differences, non-invasive

testing should be performed to rule out common causes. Initial investigations should include the number of reticulocytes and blood smears to help distinguish the morphology of the cells. Further investigation should be tailored to the clinical history and examination findings, and include liver function tests, coagulation screening, viral serology, autoimmune testing, and haematology to rule out common pathologies. Management is usually aimed at the underlying cause. Blood smears associated with malignancy should be immediately referred to a haematologist for further imaging and biopsy.

Complications

Complications of pancytopenia include an increased risk of infection, life-threatening anemia, and bleeding. Patients with fever will need broad-spectrum antibiotics and anti-fungals. Supportive transfusions with red blood cells and platelets should be started immediately if severe anemia or thrombocytopenia accompanied by bleeding occurs. Other complications include tumor lysis syndrome seen in patients receiving chemotherapy for large tumors such as high-grade lymphoma and acute leukemia.

RESEARCH METHOD

The research method used in this study is a case study method, focusing on the analysis of patient cases diagnosed with pancytopenia et causa suspected aplastic anemia. Data were collected through a series of patient examinations including anamnesis, physical examination, supporting examinations, and laboratory results, followed by therapy management in the hospital. Anamnesis identified the patient's main complaints and previous medical history and treatment, while a comprehensive physical examination included vital signs, general status, and systemic organ examination. Supporting examinations such as complete blood count, blood chemistry tests, and abdominal ultrasonography were used to evaluate the patient's hematological condition in detail. Furthermore, the data were processed and analyzed to determine the effectiveness of medical interventions given during the treatment period and the impact of transfusion therapy on improving the patient's condition, which was achieved at the time the patient was discharged from the hospital.

Table 7. Laboratory Results on 04/10/2024

Examination	Result	Normal Value
CBC		
Leukocyte	1.060	3,600 – 11,000 /ul
Erythrocyte	580.000	3,800,000 – 5,200,000 /ul
Hemoglobin	2,1	11.7 – 15.5 gr/dl
Hematocrit	6,9	35,0 – 47,0 %
Platelets	76.000	150,000 – 450,000 /ul
MCV	119	80-100 fL
MCH	36,2	26.0-34.0 pg
MCHC	30,4	32.0 – 36.0 gr/dl
RDW-SD	92	37 – 54 fL
RDW-CV	21,6	11 - 16 %
CLINICAL CHEMISTRY		
Urea	21,0	10.0 – 50.0 mg/dl
Creatinine	0,9	0.6 – 1.0 mg/dl
Blood Glucose During	101	<200 mg/dl
SGOT	66,7	<40 U/L
SGPT	11,6	<40 U/L
DIFF COUNT		
Neutrophils	54,5	42,0 – 74,0 %

Lymphocytes	27,3	17,0 – 45,0 %
Monocytes	0,0	5,0 – 12,0 %
Eosinophils	0,0	2,0 – 4,0 %
Basophils	18,2	0 – 1 %
Absolute Lymphocytes	0,03	0,90 – 5,20 %
BLOOD		
Blood Type	B	
Rhesus	Positive	

Table 8. Laboratory Results on 06/10/2024

Examination	Result	Normal Value
Anti HIV Rapid	Non Reactive	Non Reactive
HbsAg	Negative	Negative
Anti HCV	Negative	Negative

Table 9. Laboratory Results on 07/10/2024

Examination	Result	Normal Value
CBC		
Leukocyte	1.920	3,600 – 11,000 /ul
Erythrocyte	3.250.000	3,800,000 – 5,200,000 /ul
Hemoglobin	10	11.7 – 15.5 gr/dl
Hematocrit	29,1	35,0 – 47,0 %
Platelets	83.000	150,000 – 450,000 /ul
MCV	89	80-100 fL
MCH	30,8	26.0-34.0 pg
MCHC	34,4	32.0 – 36.0 gr/dl
RDW-SD	49	37 – 54 fL
RDW-CV	18,2	11 - 16 %

1. Diagnosis

- Early Diagnosis in the Emergency Room : Anemia, Pancytopenia
- Diagnosis of Asthma : Pansitopenia et causa susp Aplastic Anemia

2. Governance

Therapy in the emergency room

- O2 3 LPM
- Install Transfusion Set
- IVFD RL 20 tpm
- Check Lab CBC, Ur, CR, GDS, EKG
- Consul of DPJP

Table 10. Patient Care Doctor (dr. Ibnu Mas'ud, Sp.PD) Patient Journey

Date and Room	Results of Assessment and Service Delivery (SOAP)	Instructions for Health Workers	Other Remarks
04/10/2024 Bougenvile Room	S/ complaints of weakness since 1 week of SMRS, itching in the legs and buttocks. O/ ku : medium ; Case : CM TD : 130/80 mmhg N : 82 x/min RR : 20 x/min	DPJP Advice - O2 room air - IVFD asering 500cc/8 hours - Regular diet 1700 kcal - IV OMZ 1x1 amp - IV melamelamine 1x1	The results of the CBC, UR, CR, SGOT, SGPT and Diff Count Labs are attached to the supporting examination.

	T: 36.6 Celsius SpO2 : 99% with O2 support A/ Anemia, pancytopenia P/Therapy according to DPJP	- Sucralfat syr 3x10ml - PRC transfusion 1000 cc gradually 2 kolf a day, premed target difehydramine Hb 8	
05/10/2024 Bougenvile Room	S/ complaints of weakness, dizziness. O/ ku : medium ; Case : CM TD : 138/82 mmhg N : 64 x/min RR : 20 x/min T: 36.9 Celsius SpO2 : 99% room air A/ Pansitopenia susp aplastic anemia P/Therapy according to DPJP	DPJP Advice - O2 room air - IVFD asering 500cc/8 hours - Regular diet 1700 kcal - IV OMZ 1x1 amp - IV melamelamine 1x1 - Sucralfat syr 3x10ml - PRC transfusion 1000 cc gradually 2 kolf a day, premed target difehydramine Hb 8	Transfusion 2 colf per day, premed diphenhydramine 1 amp/colf. Transfusion enters the 3rd and 4th colfs.
06/10/2024 Bougenvile Room	S/ complaints of weakness (reduced), bleeding (-). O/ ku : medium ; Case : CM TD : 132/76 mmhg N : 66 x/min RR : 20 x/min T: 37.4 Celsius SpO2 : 99% room air A/ Pansitopenia susp aplastic anemia P/Therapy according to DPJP	DPJP Advice - O2 room air - IVFD asering 500cc/8 hours - Regular diet 1700 kcal - IV OMZ 1x1 amp - IV melamelamine 1x1 - Sucralfat syr 3x10ml - PRC transfusion 1000 cc gradually 2 kolf a day, premed target difehydramine Hb 8	Transfusion 2 colf per day, premed diphenhydramine 1 amp/colf. Transfusions enter the 5th and 6th colfs.
06/10/2024 Bougenvile Room	S/ complaints of weakness (reduced), proposal to the DPJP for other supporting examinations O/ ku : medium ; Case : CM TD : 135/78 mmhg N : 65 x/min RR : 18 x/min T: 37.1 Celsius SpO2 : 99% room air A/ Pancytopenia susp anemia aplastic dd/ B12 deficiency P/ -Therapy according to DPJP -proposal to check HIV, HCV, HbsAg lab	- ACC - Add Abdominal Ultrasound and MDT -> MDT is canceled because it has been transfused	The results of HIV, HbsAg, HCV checks are attached. Transfusions enter the 7th and 8th colfs.

08/10/2024 Bougenvile Room	S/ complaints of weakness (reduced). Appetite recovers. O/ ku : medium ; Case : CM TD : 132/76 mmhg N : 66 x/min RR : 20 x/min T: 37.4 Celsius SpO2 : 99% room air A/ Pansitopenia susp aplastic anemia P/Therapy according to DPJP	DPJP Advice - O2 room air - IVFD asering 500cc/8 hours - Regular diet 1700 kcal - IV OMZ 1x1 amp - IV melamelamine 1x1 - Sucralfat syr 3x10ml - PRC 1000 cc daily gradual transfusion 2 kolf, premed difehydramine - Target Hb 8 - Extra Ca Gluconas 1 amp	Abdominal ultrasound today, abdominal ultrasound readings in supporting examinations.
09/10/2024 Bougenvile Room	S/ no complaints of weakness. Appetite recovers. Patients have no complaints. O/ ku : good; Case : CM TD : 137/78 mmhg N : 60 x/min RR : 20 x/min T: 37 Celsius SpO2 : 99% room air A/ Pansitopenia susp aplastic anemia P/Therapy according to DPJP	DPJP Advice - Outpatient - Home medicine: cefixime 2x200mg, folic acid 1x1, omeprazole 2x1, paracetamol 3x500mg	Patients Discharged

RESULT AND DISCUSSION

The patient, a 58-year-old man, came to the emergency room of Batang Hospital with the main complaint of weakness. Weakness has been experienced since 1 week of SMRS. Nausea (+), vomiting (-), vomiting blood (-). Eat and drink as usual. It is said that they eat vegetables and meat such as chicken and eggs on a daily basis. Fever is absent. Cough is absent. Weight loss is non-existent. Normal bowel movements, blood bowel movements denied. Normal BAK, red bak is denied. The previous disease history was a patient with a history of 2 transfusions, the first at Batang Hospital and the second at QIM, previously treated with dr. Ibnu, Sp.PD with a diagnosis of pancytopenia. A history of hypertension and diabetes is denied. A previous history of severe illness was denied. A family history of disease that had similar complaints was denied. History of drug use/treatment denied. On physical examination both the general state and vital signs are within normal limits. In the examination of generalized status, the abnormal results were on the lips appearing pale, the eye conjunctiva anemone, and the extremity appearing pale. There is no murmur in cardiac auscultation and no organomegaly such as hepatomegaly or splenomegaly is palpable in abdominal palpation examination.

Pancytopenia, a clinical-hematological entity, is a bone marrow disorder that is often encountered in clinical practice. Pancytopenia is more of a clinical manifestation due to a spectrum of diseases that affect bone marrow and/or white blood cells (WBCs), red blood cells (RBCs), and platelets, rather than a disease entity. Depending on the severity of anemia, leukopenia, and thrombocytopenia, the clinical presentation varies. General weakness, fever, weight loss, abnormal bleeding tendencies, shortness of breath, etc., are

common manifestations of pancytopenia, and the prognosis depends on a correct and timely diagnosis of the underlying etiology (Gajbhiye et al., 2022).

The symptom experienced by this patient is weakness. This is in accordance with the theory that the most common throbbing is fatigue, followed by fever and a tendency to bleed. In this patient, there were no risk factors for food deficiency, although no standard questionnaire was used, but anamnesis performed several times on the patient showed that the patient's food intake included balanced nutrition. The patient does not experience fever, which likely indicates that no infection has occurred in this case. And only anemia causes complaints to appear, namely weakness.

This is in accordance with the theory. Clinical presentation can vary, with mild asymptomatic pancytopenia to life-threatening emergencies in severe pancytopenia. Symptoms appear due to impaired cell function involved, and include fatigue, infection, and bleeding. However, pancytopenia is often only identified on a blood test because of its non-specific presentation. Patients may show manifestations of one of the declining cell lines.

Unfortunately, in this patient, a thoracic X-ray examination was not performed, so data from this support did not exist. The results of the ECG showed a normal rhythm of the sinus rhythm with a heart rate of 75 x/min. Even so, the anamnesis and physical examination did not show any abnormalities in the patient's heart and lungs. An abdominal ultrasound examination on October 7, 2024 showed no abnormalities in the intraabdominal organ sonography, which indicates that there are no organomegaly and no abnormalities in the patient's liver. The other examination was a separate blood laboratory 3 times, the first when in the emergency room, the second when in the room on October 6, 2024, and the third in the room on October 7, 2024 before the patient went home.

The first blood laboratory support examination will be on October 4, 2024. Abnormal results were obtained from all complete blood results, ranging from leukopenia (1,060/ul), low erythrocytes (580,000/ul), anemia gravis (2.1 gr/dl), low hematocrit (6.9%), thrombostiopenia (76,000/ul), erythrocyte morphology examination obtained MCV 119 fL, MCH 36.2 pg, MCHC 30.4 gr/dL and RDW-CV 92 fL and RDW-SD 21.6%. The results of kidney function were normal, the results of liver function were slightly improved in SGOT (66.7 U/L), and the GDS examination with *glucostick* was obtained normal with 101 mg/dl. The *Differential Count* examination obtained a decrease from monocytes (0.0%), absolute lymphocytes 0.03%, and an increase from basophils by 18.2%. The second blood laboratory supporting examination on October 6, 2024, obtained results of anti-HIV rapid, HbsAg and normal anti-HCV, namely nonreactive or negative. The third blood laboratory support examination on October 7, 2024, obtained results of leukopeni (1,920/ul), low erythrocytes (3,250,000/ul), improved mild anemia (10 gr/dl), thrombocytopenia (83,000/ul) and erythrocyte morphology that returned to normal.

Regarding the clinical manifestations of pancytopenia, pancytopenia is a manifestation of various malignant and non-malignant primary clinical abnormalities. Decreased hematopoietic cell production, such as in aplastic anemia, abnormal cells that infiltrate the bone marrow, such as in hematological malignancy, autoimmune disorders, hypersplenism, excessive cell destruction due to ineffective production such as in megaloblastic anemia, and others are some of the many possible mechanisms behind the development of pancytopenia. In this patient, the condition at the beginning of admission with erythrocyte morphology that increases and enlarges both MCV, MCH, and MCHC. From this morphology, it is concluded that the patient has macrocytic/megaloblastic anemia.

The diagnosis in this patient at the beginning is anemia and pancytopenia which then changes to pancytopenia et causa suspected aplastic anemia. Pancytopenia is established based on a complete blood examination when the patient is admitted to the hospital characterized by complaints of weakness and a previous history of transfusions accompanied by similar complaints.

Once pancytopenia is confirmed at the beginning of a complete blood count, an initial non-invasive examination should be performed including a reticulocyte count and a blood smear. The reticulocyte count is a good substitute indicator for bone marrow response, where a low reticulocyte count will lead to bone marrow production disorders, while an increased reticulocyte count will indicate peripheral damage.

The instructions that are available in our limited health facilities can only be obtained in the form of general examinations in the form of blood chemistry (kidney function), complete blood and leukocyte type counting. The morphology of erythrocytes in this case is a large erythrocyte cell or often called megaloblastic/macrocytic. Macrocytic or megaloblastic anemia should be checked for B12 and reticulocyte reserves, but this cannot be done in this case. According to Anis H (2023), megaloblastic anemia can be caused by a deficiency of vitamin B12 and folic acid. This condition is caused by impaired DNA synthesis, which inhibits nuclear cleavage. The maturation of the cytoplasm, which mainly relies on the synthesis of RNA and proteins, becomes lacking and disrupted. This leads to asynchronous maturation between the nucleus and the cytoplasm of the erythroblas, which explains the large size of the megaloblasts (Hariz & Bhattacharya, 2019).

Referring to the diagnosis algorithm in patients with pancytopenia, several things can be concluded and studied from this patient. In anamnesis where it is not found or has been eliminated, the possibility of the influence and effect of drugs/toxins entering the patient's body is eliminated. And the physical examination did not have splenomegaly and hepatomegaly which indicated the possibility of not having hyperslenism and this was also supported by an abdominal ultrasound examination where the patient's splen and liver were normal, showing the conclusion that pancytopenia is not a peripheral type / destruction type and is not caused by a case of anemia due to megaloblastic / subleukemic leukoemia case.[6] There is no enlargement of the lymph / lymphadenopathy which means that the patient is most likely not infected and does not develop lymphoma (Island, 2021a). From the physical examination, it can be indicated that the patient may be of the central type, in this patient also has macrocytosis on the erythrocyte morphology examination which shows the possibility of dysfunction of the bone marrow. Although according to (Rao, 2011) Splenomegaly and hepatomegaly are seen in cases of megaloblastic anemia, followed by subleukemic leukemia and malaria. Bone pain is seen in multiple myelomas. Lymphadenopathy is seen in subleukemic leukemia – a type of lymphoblast.[6] However, from the algorithm this requires an examination to determine whether it is due to destruction or due to frequent intake of bone marrow failure, which requires checking the number of reticuloccytes.[5] In patients, there is also no possibility of intake deficiency/abnormality of nutrient intake, so it is likely that the megaloblastic that occurs is most likely the result of hypocellularity of the bone marrow due to aplastic anemia. Even so, a bone marrow biopsy examination and counting the number of reticulocytes need to be done to distinguish whether the cause is non-nutritional or nutritional.[7] In this patient, morphological data on peripheral blood at the beginning were not obtained. Screening for infections such as HIV, HbsAg and HCV showed negative results, indicating that there were no chronic infections most commonly associated with pancytopenia. So in the final conclusion on the macrocytic morphology of this patient, which is not accompanied by problems in kidney function, indicates that it is likely that the pancytopenia experienced by the patient is likely to be caused by aplastic anemia or myelodysplasia with another differential diagnosis of vitamin B12 deficiency. Even so, the diagnosis of etiology definitely requires a biopsy of the bone marrow and a reticulocyte examination.

Aplastic anemia

Aplastic anemia is caused due to a decrease in the number of bone marrow cellularity. Most of the case causes of aplastic anemia are idiopathic and some cases are related to infections, drugs, toxins, radiation, or pregnancy.The pathophysiology that occurs is in the stem cells and the inability of the bone marrow tissue to give the stem cells

a chance to grow and develop properly. This is closely related to mechanisms that occur such as direct toxicity or deficiency of stromal cells.[2]

Aplastic anemia refers to a chronic primary hematopoietic failure syndrome due to injury that results in a reduced or absence of hematopoietic precursors in the bone marrow and accompanying pancitopenia. Also called fanconi anemia, a condition of anemia caused by heredity. Aplastic anemia appears at all ages with an equal distribution across genders and races. Symptoms are associated with the absence of a cell lineage (anemia, progressive weakness, paleness, and dyspnea; neutropenia, frequent and persistent mild infections, or febrile illness that arises suddenly; thrombocytopenia, echymorrhage, mucosal hemorrhage, and petekie). Splenomegaly is not visible, and its presence suggests an alternative diagnosis. The laboratory will show macrositer normochromic anemia with reticulopodia, neutropenia, and thrombocytopenia. There should be no cytological abnormalities as this will indicate the underlying hematological processes.[10] The presence of splenomegaly or anisocytosis, or the absence of mild macrocytosis, makes the diagnosis of aplastic anemia impossible. Lymphadenopathy is also uncommon in aplastic anemia, and infection should be considered instead. Aplastic anemia should be diagnosed by bone marrow aspiration and *trephine biopsy*.[5]

The diagnostic criteria for aplastic anemia are: the presence of hypocellularity of the bone marrow and 2 or more cytopenia (reticulopodia of less than 1% or less than 40,000/microliter, neutropenia of less than 500/microliter, or thrombocytopenia of less than 20,000/microliter). "moderate" disease has bone marrow cellularity of less than 30%; "severe" disease has a cellularity of less than 25% or a cellularity of less than 50% of the 30% of cells containing hematopoietic cells; and "very severe" diseases that meet the criteria of "severe" plus neutropenia of less than 200/μL. A bone marrow biopsy is very important: the biopsy will be highly hypocellular and have no progenitor cells/source from the bone marrow. Genetic testing with *flow cytometry and fluorescence hybridization in situ* (FISH) is useful to rule out hematological malignancies that cause pancytopenia. Additional testing depends on the underlying condition that caused bone marrow failure, e.g. testing for telomerase mutations for congenital dyskeratosis (Island, 2021b).

The management of aplastic anemia is aimed at the underlying cause. If possible is to get rid of the agent that can cause it. Some drugs have been discontinued in the United States due to their association with aplastic anemia (e.g., Ticlopidine, a platelet aggregation inhibitor used as a primary/secondary stroke prevention or double antiplatelet therapy after percutaneous coronary intervention; phenylbutazone, an NSAID used as an analgesic and antipyretic). Aplastic anemia associated with pregnancy resolves on its own and ends after childbirth. Patients with thymoma usually experience full bone marrow recovery after thymectomy. For patients with no reversible cause found, treatment depends on age, disease severity, donor availability, and physical activity status. Healthy young patients (under 50 years) with severe disease should undergo allogeneic Hematopoietic Cell Transplantation (HCT) prior to initial immunosuppressive therapy. Healthy older patients (50 years or older) and young patients without HCT donors received full-dose immunosuppressive therapy using eltrombopag, equine/rabbit antithymocyte globulin (ATG), cyclosporin A, and prednisone. This combination can be adjusted with single-agent elthrombopag, ATG, or cyclosporin A for less healthy individuals. Eltrombopag is a nonpeptide agonist of thrombopoietin that increases platelet count and activates intracellular signal transduction pathways to enhance the proliferation and differentiation of bone marrow progenitor cells. ATG removes antigen-reactive T lymphocytes and induces a hematological response in aplastic anemia. Cyclosporin A inhibits the production and release of interleukin-II (IL-2) and inhibits IL-2 activation induced by T. Prednisone lymphocytes induces the death of immature lymphocyte cells. Clinical studies are being conducted for alternative therapies used as second-line agents. Supportive care includes prophylaxis/infection treatment and transfusions (red blood cells with a decrease in leukocytes for Hb less than 7 mg/dL or platelets less than 10,000/microliter or less than

50,000/microliter for active blood loss). Monitor secondary hemochromatosis and provide iron chelation as indicated. The use of growth factors such as erythropoietin or granulocyte colony stimulating factors is not recommended because there are not enough precursor cells to produce an adequate response.

Survival in aplastic anemia is highly dependent on age, disease severity, and response to initial therapy. Those who recover after discontinuation of medication or treatment of underlying conditions have a stable clinical course, as do those who have a self-healing process. Five-year survival is greater than 75% for patients undergoing bone marrow transplants from suitable donors. The majority of untreated patients die within one year from disease-related complications (e.g., bleeding, infection, or transformation into lymphoproliferative disorders).

Myelodysplastic syndrome (MDS)

Myelodysplasia syndrome is a syndrome of abnormalities of blood *stem cells* characterized by impaired proliferation and maturation of hematopoesis cells. Myelodysplasia syndrome is a group of myeloid neoplasms characterized by cytopenia due to ineffective hematopoiesis, abnormal bone marrow blood morphology and risk of developing acute myeloblastic leukemia. Infection, bleeding and anemia are common descriptions in MDS, while the unusual ones are hepatomegaly, splenomegaly and lifadenopathy (Oktariani et al., 2020).

Myelodysplastic syndrome (MDS) is a diverse collection of hematological neoplasms characterized as clonal abnormalities of hematopoietic stem cells, resulting in dysplasia and ineffective hematopoiesis in the bone marrow. This condition often causes varying degrees of cytopenia, which can manifest as anemia, leukopenia, or thrombocytopenia. Some individuals with MDS may develop acute myeloid leukemia (AML), further complicating their clinical journey (Dotson & Lebowicz, 2018).

The progression of MDS can occur due to various mechanisms such as environmental exposure to chemicals such as benzene, radiation, previous exposure to chemotherapy agents, or may be idiopathic, which is usually seen in the elderly population. Bone marrow failure syndromes such as acquired aplastic anemia and Fanconi anemia have a risk of developing MDS and sometimes resemble this syndrome. MDS can occur de novo or secondary as a result of other causes, also known as treatment-related MDS (Dotson & Lebowicz, 2018).

Diagnosis of MDS requires evaluation of peripheral blood and bone marrow histopathology with aspiration and bone marrow biopsy. MDS can be suspected if one or more cytopenia is present. According to the guidelines of the International Working Group for MDS, there are 2 prerequisite criteria for diagnosis: (1) stable cytopenia for 6 months or more, or 2 months if a specific karyotype or bilineage dysplasia is present, and (2) the exclusion of other causes of dysplasia and/or cytopenia. Anemia is the most common manifestation of MDS, which may be normociter or macrositer. Evaluation of other potential causes of anemia should be performed with additional laboratory testing, including iron and ferritin levels, B12 and folate levels, hemolysis examination with lactate dehydrogenase, haptoglobin and Coombs testing, and serum protein electrophoresis and immunosuppression as part of multiple myeloma examination, if clinically applicable. Zinc and copper deficiency is the cause of rare nutrients from anemia that can resemble MDS. Macrocytosis is commonly seen in MDS but is usually unresponsive to B12 or folate replacement. Neutropenia and/or thrombocytopenia can also be seen in anemia or later in the course of the disease. Initial evaluation includes a complete blood count with differential, peripheral blood smear, and other clinically relevant laboratory investigations. Diagnostic evaluation should also include bone marrow biopsy and aspiration, immunophenotype flow cytometry, cytogenetic evaluation with karyotype and fluorescence hybridization in situ (FISH, along with genetic profiling (performed with genomic profiling) to assess relevant somatic mutations such as *SF3B1*, *TET2*, *SRSF2*,

ASXL1, *DNMT3A*, *RUNX1*, *U2AF1*, *TP53*, and *EZH2* (Dotson & Lebowicz, 2018); (Indayanie & Rachmawati, 2015).

Megaloblastic anemia

Megaloblastic anemia includes a group of heterogeneous macrostyric anemias characterized by the presence of large red blood cell precursors called megaloblasts in the bone marrow. This condition is caused by impaired DNA synthesis, which inhibits nuclear cleavage. The maturation of the cytoplasm, which mainly depends on the synthesis of RNA and proteins, is less disturbed. This leads to asynchronous maturation between the nucleus and the cytoplasm of the erythroblas, which explains the large size of the megaloblasts. This process affects hematopoiesis as well as rapid tissue renewal such as gastrointestinal cells. Megaloblastic anemia is most commonly caused by hypovitaminosis, specifically a deficiency of vitamin B12 (cobalamin) and folate, which is necessary for DNA synthesis. Copper deficiency and adverse drug reactions (due to drug interference in DNA synthesis) are other well-known causes of megaloblastic anemia. A rare hereditary disorder known as thiamine-responsive megaloblastic anemia syndrome (TRMA) has also been identified as the cause of megaloblastic anemia. The list of drugs associated with this disease is long, however, the agents that are often involved include hydroxyurea, chemotherapy agents, anticonvulsants, and antiretroviral therapy (ART) drugs.[9 reviews]

The main food sources of cobalamin/vitamin B12 are meat, fish, eggs, and dairy products. A vegan diet low in vitamin B12. Folic acid is found in foods such as green vegetables, fruits, meat, and liver. The daily requirement of an adult ranges from 50 to 100 mcg. The recommended nutritional adequacy figure is 400 mcg in adults and 600 mcg in pregnant women. Folic acid is mainly absorbed in the jejunum and the body stores about 5 mg of folate in the liver, which is enough for 3 to 4 months. Folic acid deficiency can be associated with a decrease in intake in cases of alcohol use disorders or malnutrition (elderly patients, patients treated in institutions, poverty, special diets, etc.), an increase in demand especially in cases of pregnancy, hemolysis, hemodialysis and malabsorption (tropical diseases, celiac diseases, jejunum resection, Crohn's disease, etc.). In some cases, medications such as anticonvulsants and anticancer agents cause megaloblastic anemia associated with folate deficiency by affecting folate metabolism.[9 reviews]

Clinical suspicion for megaloblastic anemia should be high in patients with unexplained macrositer anemia (mean corpuscular volume [MCV] greater than 100 fL) or hypersegmentation neutrophils on peripheral smears. MCVs greater than 115 fL are more specific for vitamin B12 deficiency or folate deficiency than other causes of macrocytosis, however, normal MCVs do not rule out megaloblastic anemia. Count of reticucytes is also indicated in the examination of this disease. In patients with typical peripheral blood smear findings and low reticulocyte counts, the only tests required are vitamin B12 and serum folate levels. In patients who eat a normal diet, folate levels can be negligible. In patients with suspected absorption disorders or malnutrition such as excessive alcohol consumption, both levels must be obtained. B12 levels above 300 pg/mL (above 221 pmol/L) are considered normal. Levels between 200 to 300 pg/mL (148 to 221 pmol/L) are considered the limit and additional testing must be performed to verify the diagnosis and explain the cause. Levels below 200 pg/mL (below 148 pmol/L) are consistent with deficiency and further testing is only indicated if the route of administration of B12 supplementation needs to be clarified.[9 reviews]

Of the many possible etiologies in our patients, the most likely is due to the central type, more specifically the possibility of aplastic anemia or malignancies such as myelodysplasia syndrome and other blood malignancies, which require further examination. Even so, if there is an opportunity, perhaps researchers will conduct further examinations. Because according to Osman Yokus and Habip Gedik from a study of 137 cases of pancytopenia etiology at the Istanbul Training and Research Hospital, it was obtained for the age of this patient 58 years old which is under 65 years old and the male

gender, the most frequent cause of pancytopenia is Vit B12 deficiency, then aplastic anemia, and the last is due to malignancy.[5]

But in the end, the researcher wants to say that although it is most likely the cause is a central disorder, it can still be wrong. It is argued that although the causes of pancytopenia can be mostly grouped into peripheral cell damage disorders, or disorders of bone marrow production. However, most conditions tend to exhibit the characteristics of both, as pancytopenia can arise from a variety of different pathophysiological mechanisms.[4]

The therapy that the patient gets during treatment is O2 with room water, then Infusion with transfusion set asering 500cc/8 hours, Regular diet with 1700 kcal, OMZ 1x1 amp injection, Mecobalamin 1x1 injection, Per oral Sucralfat syr 3x10ml, and PRC Transfusion program 1000 cc gradually 2 kolf a day, premed difehydramine, with a minimum target of Hb 8. In patients, room treatment turns out that patients need PRC transfusions of more than 1000 cc/ 4 kolf, in patients get transfusions of up to 8 colf (2000 cc) with transfusions of 2 kolf per day with premed diphenhydramine and HB 8 targets. And during the 5th day of treatment (from October 4 to 8, 2024), the patient felt that there were no more complaints and was given HB 10, and it was on target, so the patient was discharged.

This patient is given omeprazole therapy, which is a group of protome pump inhibitors (PPIs) that are often used to manage and treat conditions such as heartburn, peptic ulcer disease, GERD disease, and helicobacter pylori infection.[13] Of these patients, although long-term use is not recommended, it is likely that omeprazole is used for prophylactic therapy which is expected to reduce the risk of erosive gastric disease due to low platelet patients. Mecobalamine is another form of vitamin B12, which functions for the formation of red blood cells to be good for nerve cells. Useful for megaloblastic anemia, peripheral neuropathy and pinched nerves. In this patient, antibiotic therapy was not given as should be according to the procedure given for prophylactic therapy, it was not given possibly because there were no signs of infection and a previous history of repeat with the same complaint made it possible that the cause was of the central type so that the administration of antibiotics was not so necessary.

In this patient, a PRC transfusion of 1000 cc with premed difenhydramine 1 amp/kolf (approximately 250 cc) is planned. Transfusion is a supportive therapy for the management of a decrease in one of the 3 blood cells, namely red blood cells/hemoglobin. And in this patient, the focus for management is Hb improvement with PRC transfusion. And in this case, it is appropriate to give PRC transfusion only, because for platelets there is no indication to transfuse at that time (platelet level 76,000). Transfusions may also be indicated in patients with active or acute bleeding and patients with symptoms associated with anemia (e.g., tachycardia, weakness, dypnea during activity) and hemoglobin less than 8 g/dL.[14] In the administration of blood transfusions to increase Hb levels by 1 gr/dL, PRC 4 mL/kgBB or one (1) unit can increase hematocrit levels by 3–%. The substance is administered for two (2) to four (4) hours at a rate between 1–2 mL/minute, with known ABO and Rh blood types.[15] in this patient, the initial plan given was PRC 1000 cc or 4 colf, which required 8 colf or around PRC 2000 cc, only obtained results that exceeded the initial target of 8 gr/dl and the result at the end of the post-transfusion was 10 gr/dl at a complete blood test 1 day before the patient went home.

Most cases of pancytopenia can be cured with specific treatment tailored to the cause and severity of the disease or, sometimes, the case requires timely supportive treatment to reduce morbidity and mortality, thereby improving the patient's quality of life.[8] supportive treatments for patients include red blood cell transfusions for anemia to relieve geja and perfusion of the body's vital structures. Platelet transfusions are indicated for thrombocytopenia of less than 10,000 per mL to prevent spontaneous intracranial bleeding. Broad-spectrum antibiotic therapy should be started immediately for patients with neutropenia fever or severe neutropenia with an absolute neutrophil count of less than 500 per ml due to the risk of death from sepsis.[1]

Treatment should be based on the underlying etiology of pancytopenia. Nutritional deficiencies must be corrected. Any medication that triggers pancytopenia (methotrexate, linezolid, or anticonvulsant) should be discontinued immediately. Treatment for infections such as HIV or tuberculosis should be started immediately. If an autoimmune condition or malignancy is diagnosed, it should be treated.[1,2] Because the underlying pathology determines the treatment and prognosis of patients with pancytopenia, identification of the cause is crucial. Pancytopenia and aplastic anemia are no longer as identical as previously thought. There has been a definite trend change from aplastic anemia to megaloblastic anemia over the years. Megaloblastic anemia is quite common in the Indian population, probably due to nutritional factors and is easily cured with proper treatment. Thus, megaloblastic anemia should always be considered in the evaluation of pancytopenia in India and other Asian countries. Evaluation of patients with pancytopenia requires a holistic approach and identification of the underlying cause remains a challenge due to varied etiopathological factors and inherited conditions. Recent advances in molecular pathology including genomic profiling and next-generation sequencing have great potential in providing cost-effective diagnostic options in such cases and need to be explored with proper emphasis.[7]

CONCLUSION

Identification of the cause is very important for patients with pancytopenia, as the underlying pathology will determine the treatment and prognosis of the patient. It has been reported that a 58-year-old male patient with the main complaint of weakness experienced since 1 week, no signs of infection, no signs of bleeding, no signs of chronic disease, and no history of drug consumption or previous chronic treatment. It was only found that the patient had a history of transfusion 2 times, even a family history of diseases that had similar complaints was also absent. Determining the etiological diagnosis in this case is difficult to do due to the lack of supporting examinations, but from the anamnesis, physical examination and supporting examinations carried out, there is a possibility that this patient has central type pancitopenia, and the primary type type. Then this patient received supportive management in the form of PPIs, mecobalamin which is a vitamin B12 agent, and blood transfusions to be able to reduce the symptoms experienced by the patient. This is appropriate where transfusions, and the administration of vitamin B12 agents will help improve the clinical condition and control his macrocytic anemia. Determining the actual etiology is very important, but requires further tests such as bone marrow biopsy or reticulate examination, so that the exact diagnosis of the cause can be known and treated more appropriately and to prevent recurrence.

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