# BÖLÜM 5

# HEMATOLOGIC AND ONCOLOGIC EMERGENCIES

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Hematologic oncologic emergencies are potentially life-threatening acute complications associated with the underlying disease or associated with treatment. Hematologic oncologic emergencies occur due to local invasion of malignancies to neighboring tissues or metastasis to distant sites, loss of function and organ failure due to infiltration of parenchymal organs, metabolic disorders due to the release of various hormonal or molecular tumor materials, and immunosuppression caused by side effects of therapeutic drugs. Hematologic oncologic emergencies may present with many different clinical manifestations. These conditions can occur as a first presentation or in a patient with a certain diagnosis. Hematologic oncologic emergencies occur due to local invasion of malignancies to neighboring tissues or metastasis to distant sites, loss of function and organ failure due to infiltration of parenchymal organs, metabolic disorders due to the release of various hormonal or molecular tumor materials, and immunosuppression caused by side effects of therapeutic drugs. Since it is a situation that all physicians may encounter, they must have adequate knowledge about the diagnosis of basic hematologic-oncologic emergencies and the most appropriate treatment approaches. In this chapter, we discussed the epidemiology, pathophysiology, and treatment of these conditions with the principles of the hematological approach (1,2).

## Hypercalcemia

*Hypercalcemia* is a condition in which serum calcium levels are higher than 3.24 mmol/lt (13 mg/dl). Hypercalcemia is prevalent in especially advanced cancer patients and is seen in approximately 20-30% of patients with malignancy (3).

Hypercalcemia is most commonly associated with multiple myeloma and non-small cell squamous cell lung cancer but may also be seen in other malignant diseases (4).

The most common cause of hypercalcemia of malignancy is parathyroid hormone-related peptide (PTHrP) secretion from the tumor. PTHrP is structurally similar to PTH, binds to the PTH receptor in osteoblasts, and stimulates nuclear factor-kB ligand (RANKL) signaling. It then causes increased osteoclastic activity,

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bone reabsorption, and elevation of serum calcium.This mechanism is generally named humoral hypercalcemia of malignancy (5-7). Humoral hypercalcemia is one of the poor prognostic factors and is less responsive to bisphosphonate therapy (8-10).

Another mechanism of hypercalcemia is bone destruction due to osteolytic bone metastases. This mechanism is particularly related to multiple myeloma. The least prevalent mechanism is the production of 1-alpha hydroxylase and 1.25 dihydroxycholecalciferol by the malignant cells. This mechanism is seen as more common in lymphoma cases. The main clinical manifestations depend on both the degree of calcium concentration and velocity of onset (11). Clinically, hypercalcemia causes muscle weakness, fatigue, nausea, vomiting, polyuria, abdominal or low back pain, and constipation. Severe hypercalcemia can cause confusion and bradyarrhythmias. Prolongation of the PR interval, enlargement of the T wave, shortening of the QT interval are observed on the electrocardiogram (ECG), and even cardiac arrest (12).

The first treatment strategy is bolus intravenous fluid administration. Relief of patients from a hypovolemic state both decreases serum calcium level and causes renal calcium excretion. 0.9% sodium chloride is preferred as a liquid. Fluid therapy of 3-6 lt/m2/day and concomitant high-dose furosemide (1-3 mg/kg/i.v. every 6 hours) is usually sufficient for treating mild to moderate hypercalcemia. Another treatment option is calcitonin, which has a rapid onset of action, inhibits osteoclasts, and increases renal calcium (13). Bisphosphonates are synthetic pyrophosphate analogs that bind to hydroxyapatite crystals and block bone resorption from osteoclasts. In bisphosphonate treatment, 2-3 days are required to see the full effect. In case of renal insufficiency, drug dose adjustment is required. Pamidronate, Zolendronate, and Ibandronate are preferred (14). Denosumab is administered at a dose of 120 mg subcutaneously every week. It can be used in patients with renal insufficiency, but the onset of action is slower than with bisphosphonates (15).

Glucocorticoids block the conversion of calcidiol to calcitriol and also lead to a reducing effect on tumor burden, especially in lymphoproliferative diseases. The onset of action on calcium levels is not rapid; therefore, glucocorticoids are given with calcitonin (16,17) Hemodialysis treatment is recommended in cases of hypercalcemia refractory to medical treatments.

## Tumor lysis syndrome (TLS)

Tumor lysis syndrome (TLS) is a series of metabolic disorders resulting from the excessive release of intracellular contents into the circulation. These metabolic

abnormalities are caused by releasing intracellular contents, ions, nucleic acids, proteins, and metabolites from degraded tumor cells. These metabolic disorders include hyperkalemia, hyperphosphatemia, hyperuricemia and hyperuricosuria, and hypocalcemia. Hypocalcemia occurs as a result of the precipitation of calcium-phosphate crystals. TLS can be seen spontaneously in cases with high kinetics and tumor burden or due to cytotoxic treatment. A high incidence of tumor lysis syndrome is very aggressive hematologic cancers such as Burkitt's lymphoma and acute leukemias (18).

The main goal is to anticipate risk patients, take necessary precautions, and prevent this life-threatening complication of TLS. The most commonly used classification of TLS is the Cairo-Bishop classification, which is determined as laboratory findings and clinical symptoms (19).

**Cairo-Bishop TLS classification:**

***A laboratory finding of tumor lysis syndrome***

- **Increase in uric acid ≥7.8 mg/dL or greater than 25% of normal value**
- **Potassium ≥6.0 mmol/L or more than 25% of normal value**
- **Increase Phosphorus ≥6.5 mg/dL (child) or ≥4.7 mg/dL (adult) or greater than 25% of normal value**
- **Calcium < 8.4 mg/dL A decrease of mg/dL or more than 25% of normal**

***Clinical finding of tumor lysis syndrome***

(Presence of laboratory findings of tumor lysis syndrome and one or more of the following criteria.)

- Kidney failure
- Cardiac arrhythmia
- Seizure
- Sudden death

Hyperkalemia is the most dangerous complication of TLS for the risk initiation of cardiac arrhythmia and sudden death. Hyperkalemia must be treated aggressively. Symptomatic hypocalcemia should be treated attentively with IV calcium gluconate to control the symptoms. Asymptomatic hypocalcemia should not be treated.

Since TLS is often preventable, appropriate hydration and uric acid levels are measured to reduce renal damage. Drugs that reduce uric acid levels are Allopurinol, Rasburicase, and Febuxostat. Allopurinol prevents the formation of xanthine and uric acid from hypoxanthine by inhibiting the xanthine oxidase enzyme. Rasburicase, a recombinant urate oxidase enzyme, converts uric acid to allantoin, 5 to 10 times more soluble than uric acid (20).

## Thrombotic thrombocytopenic purpura (TTP)

Thrombotic thrombocytopenic purpura (TTP) was first described by Moschowitz in 1925 when a young girl with a clinical condition accompanied by microangiopathic hemolysis, petechiae, hemiparesis, and fever died soon after and showed hyaline thrombi in the terminal arterioles in her autopsy. In the pathogenesis of TTP; Very large vWF multimers released from the endothelium remain attached to the endothelial cell surface, causing platelet adhesion or aggregation of platelets in the bloodstream. The ADAMTS-13 (disintegrin and metalloprotease with thrombospondin type-1) enzyme is a vWF metalloprotease that cleaves von Willebrand factor into smaller forms. Congenital TTP is seen in congenital deficiency of the protease ADAMTS-13 that degrades this multimer, while IgG-type autoantibodies against ADAMTS-13 are responsible in almost all cases of acquired TTP. Since platelet-fibrin clot in small vessels is the main pathological mechanism, TTP is a member of the thrombotic microangiopathy group of diseases. ADAMTS-13 level less than 5% is diagnostic for TTP. An ADAMTS 13 level of less than 5% is diagnostic for TTP.

The standard treatment in TTP is therapeutic plasma exchange (PLEX). In this treatment, the exchange is made with fresh frozen plasma. The patient's antibodies are both removed, and the missing ADAMTS-13 replacement is performed. The mortality rate from TTP decreased to <20% with PLEX. Steroids, rituximab, and other immunosuppressive drugs can be used in resistant cases (21). Currently, Caplacizumab is an anti-von Willebrand factor humanized single-variable-domain immunoglobulin targets von Willebrand factor (vWF) that the FDA approved in 2019 (22).

## Febrile Neutropenia

Neutropenia is the absolute value of the granulocyte count in peripheral blood under 0.5 x 109/L. In clinical practice, those whose neutrophil count is between 0.5-1 x 109/L and are expected to drop below 0.5 x 109/L within 24-48 hours due to chemotherapy are also considered neutropenic (23).

The Infectious Disease Society of America defines neutropenic fever as an oral temperature of 38.3°C or higher on a single measurement, or 38.0°C or higher sustained for more than one hour (24). Febrile neutropenia is the most common complication in patients receiving cytotoxic chemotherapy. Febrile neutropenia does not include fever due to drugs or blood and blood products. Microorganisms cause most infections in neutropenic cancer patients in the host's endogenous flora. Bacterial infections are the most common cause of infections in neutropenic patients. Major risk factors for Gram-positive bacterial infections are intra-

venous catheter use, chemotherapy-induced oral mucositis, oral herpes lesions, and quinolone prophylaxis. The most commonly isolated gram-positive bacteria are coagulase-negative staphylococci, S. aureus, and enterococci. Escherichia coli, Klebsiella spp., and Pseudomonas aeruginosa are the leading infections due to Gram-negative. Fungi can cause serious infections that can threaten the life of neutropenic cancer patients. They often cause secondary infections. Candida and Aspergillus species are the most frequently isolated pathogens in neutropenic patients. Viral infections in cancer patients are less likely to cause neutropenic fever than other microorganisms. Viruses belonging to the herpes group, especially the Herpes simplex virus and Varicella zoster virus, can be reactivated after chemotherapy and steroid use. The scoring system of "The Multinational Association for Supportive Care in Cancer" (MASCC) is the most commonly used in the risk of serious complications in febrile neutropenic patients (Table 1).

| Table 1. Multinational Association for Suportive Care in Cancer (MASCC) criteria | |
|---|---|
| Asymptomatic or Mild symptom | 5 |
| Moderate symptoms | 3 |
| Severely symptomatic or fatal | 0 |
| Absence of hypotension (SBP >90 mmHg) | 5 |
| No chronic obstructive pulmonary disease | 4 |
| Solid tumor or hematologic malignant but not infected with fungal infection | 4 |
| Absence of dehydration | 3 |
| Onset of fever outside the hospital | 3 |
| Age<60 | 2 |

Patients with a MASCC score >21, mortality 1-3%, risk serious complications less than five and are considered low-risk patients. The purpose of determining the patients as low-risk and high-risk in risk assessment is to keep low-risk patients in the hospital for a shorter time or to monitor the outpatient. In low-risk patients, the first recommended drug is the combination of amoxicillin-clavulanate and ciprofloxacin (24).

Initial assessment of febrile neutropenic patients should include at least two sets (aerobic and anaerobic), chest X-ray, urinalysis, urine culture, and throat and stool culture in symptomatic cases, skin biopsy-aspiration in suspicious lesions. Examination of pleural, peritoneal, and spinal fluids should also be performed when necessary.

The most commonly used antibiotics in empirical antibiotic treatment in patients with neutropenic fever are cefoperazone sulbactam, piperacillin-tazobac-

tam, meropenem, and imipenem. The addition of aminoglycosides to antibiotics to increase their effectiveness and prevent the development of resistance is not recommended for more than 3-4 days unless bacteremia or pseudomonas infection is detected (25). If the fever persists for more than five days despite appropriate antibacterial therapy, the addition of antifungal drugs is recommended (26). The effects of amphotericin B, itraconazole, and caspofungin were similar in the empirical antifungal treatment of patients with neutropenic fever. Voriconazole should be preferred, especially when invasive aspergillus is suspected (27,28).

### Acute blood transfusion reactions

Acute blood transfusion reactions develop within 24 hours of blood or blood product transfusion. It can be seen in varying severity from minor febrile reactions to life-threatening hemolytic or hypotensive reactions. Immunological transfusion reactions occur when transfused erythrocytes, leukocytes, platelets, and plasma proteins stimulate antibody production in the recipient. Non-immunological reactions occur due to the physical and chemical properties of the transfused blood product.

### Acute hemolytic transfusion reaction (AHTR)

It is characterized by intravascular hemolysis that occurs in a short time following inappropriate blood transfusion. Most AHTRs are bound to a red cell suspension. It is usually caused by the accidental insertion of another patient's blood into the patient. Symptoms begin within a few minutes or a few hours after starting a transfusion of inappropriate blood. The main symptoms are restlessness, fever, chills, vomiting, chest and back pain, dyspnea, tachycardia, and urticaria.

The first step in treatment is to terminate the transfusion.

The transfused blood and the blood sample taken from the patient should be sent to the blood bank. The records of the compatibility tests performed before the transfusion should be checked, and the cross-match process should be repeated with the blood groups. If the signs of hemolysis are mild, it is sufficient to provide the patient's urine output with fluid and diuretic therapy. Steroid therapy may be required. In severe cases, high doses of steroids, oxygen, adrenaline, or dopamine may be required to maintain cardiac output. Therapeutic erythrocyte exchange can be performed in resistant cases (29).

### Febrile non-hemolytic transfusion reaction (FNHTR)

It is one of the most common transfusion reactions. It occurs between 30 minutes and several hours after transfusion. An increase in body temperature of more than one °C and headache are the most important findings, regardless of any other rea-

son. It is dependent on immune reactions against platelet, leukocyte antigens, and plasma proteins. The clinical picture can be confused with acute hemolytic transfusion reaction, transfusion-related acute lung injury ( TRALI), and bacteremia. Therefore, transfusion should be interrupted when a febrile reaction occurs, and a differential diagnosis should be made. It is sufficient to control the fever with antipyretics in the treatment.

### Allergic transfusion reaction

The incidence of allergic transfusion reaction is 1-2%. There may be simple findings such as itching and urticaria or life-threatening bronchospasm, angioneurotic edema, and anaphylactic reaction (30).

An anaphylactic reaction is more likely to occur when a blood product from a donor with a normal IgA level is given to a patient with IgA deficiency (31). Histamine is the primary mediator of the allergic response. Mild cases can be controlled by administering antihistamines. However, in the presence of bronchospasm, angioneurotic edema, or anaphylactic reaction, anaphylaxis treatment should be administered.

### Transfusion-related circulatory overload (TACO)

Hypervolemia should be considered if dyspnea, cyanosis, orthopnea, severe headache, hypertension, and congestive heart failure develop during or immediately after transfusion. Diuretics and oxygen are often used in their treatment. If symptoms do not improve, aggressive treatment (phlebotomy) may be required (32).

### Sickle cell disease emergency

A single point mutation at position 6 of the β chain causes sickle cell anemia (SCA). With this change, "glutamine" is replaced by "valine" and causes the formation of hemoglobin S (HbS). In hypoxia, metabolic acidosis, and infections, HbS sickles and cause occlusion in the vessels and consequently ischemia.

*Acute painful crises* are the most prominent clinical manifestation of sickle cell anemia. These events are the leading reasons for seeking emergency treatment and hospitalization. Occlusion of the microvascular system causes local pain and inflammation. There is no proven treatment for acute painful events. Treatment is symptomatic and consists of hydration and analgesia. Most painful crises can be managed with oral hydration, non-steroidal anti-inflammatory drugs (NSAIDs), non-opioid and opioid analgesics (33).

*Acute chest syndrome* is the leading cause of mortality and the second most common cause of hospitalization in sickle cell anemia. The clinical signs of acute chest syndrome are chest pain, cough, fever, hypoxia, respiratory distress, and new lesions appearing on radiological imaging (34).

*Priapism* is the unwanted, painful, persistent erection of the penis. It is seen in 5-45% of men. The cause of priapism in sickle cell anemia is venous obstruction due to vaso-occlusion. The goals of treatment are to relieve pain, treat erection, and preserve fertility. Patients are advised to increase fluid intake, use oral analgesics, and urinate and shower with warm water as soon as priapism begins. If the patient does not respond to this, erythrocyte exchange transfusion may be required (35).

*Aplastic crisis* is the most common acute hematological event. It usually appears in childhood and after a febrile illness. Most of these crises are due to parvovirus B19 infection (36). Treatment is blood transfusion if symptomatically needed.

*Spleen sequestration:* Signs of splenic sequestration are a suddenly enlarged spleen, a drop in hemoglobin of 2 grams or more, and increased erythropoiesis. Thrombocytopenia may also be seen (37). It can lead to hypovolemic shock and even death.

*Infections:* In sickle cell anemia, the spleen loses its function due to repeated vaso-occlusions. Thus, the infection rate, especially with Streptococcus pneumonia in children with sickle cell anemia, is very high compared to the general population. The risk of osteomyelitis is also higher than in the general population. The most common causes of osteomyelitis are Salmonella and Staphylococcus (38).

## HYPERVISCOSITY

*Viscosity* is defined as resistance to the flow of a liquid. The main factors affecting blood viscosity are an increase in the number of blood cells, an increase in blood proteins. The most frequent situations with a blood hyperviscosity are leukemia with hyperleukocytosis, Waldenström macroglobulinemia (WM), and multiple myeloma. Symptoms and findings of HVS are bleeding diathesis, retinopathy, neurological disorders, and congestive heart failure. The solution of the underlying cause provides the permanent treatment.

As palliative methods, leukapheresis can be applied due to cell increase, and plasmapheresis can be applied due to protein increase (39,40).

### Superior Vena Cava Syndrome

Superior vena cava superior syndrome (SVCS) is any benign or malignant pathology that compresses the superior mediastinal structures or lymphatics, obstructing blood flow through the superior vena cava. SVCS is the most common high-grade NHL in hematological disease, followed by Hodgkin's disease and T-cell lymphoblastic lymphoma/leukemia, respectively (41). lthough SVCS is seen in

2.4% to 4.2% of lung cancers, it constitutes 65-78% of all cases. Because of its central location, it is most frequently encountered in small cell lung cancer.

Non-malignant causes of superior vena cava syndrome include; fibrous mediastinitis, Tuberculosis, Histoplasma infection, a complication due to a pacemaker, and a central venous catheter (42,43).

Common symptoms and signs of SVCS include shortness of breath, orthopnea, cough, facial edema and erythema, edema of the neck and arms, dilatation of the neck and thoracic veins, headache. Diagnosis is based on the presentation of typical signs and symptoms. Diagnosis can be difficult when symptoms are unclear, and detailed imaging techniques should also be used if the diagnosis is suspected. In addition to the correct diagnosis, it is critical for the initiation of immediate effective treatment. Computed tomographical imaging with intravenous contrast is commonly used and is the most utility laboratory technique for establishing the diagnosis and revealing the etiology (44,45). Magnetic resonance imaging is especially useful in cases in which computed tomography with IV contrast is contraindicated.

In SVCS treatment, firstly, the patient should be elevated from the bedside, and temporary relief should be provided by giving oxygen support. Intubation and emergency tracheostomy may be required if the patient has stridor and respiratory failure that does not respond to corticosteroid therapy and bronchodilators.

Patients with central nervous system symptoms should be treated with dexamethasone to reduce increased intracranial pressure.

With good clinical evaluation and radiological support, empirical chemotherapy or radiotherapy is often not wrong in life-threatening situations that are not histopathologically confirmed.

Especially in cases with poor response to treatment, SVCS should bring to mind thrombosis. Anticoagulant treatment with heparin and warfarin is recommended in cases with thrombosis detected by computerized tomography or contrast tomography.

## Spinal Cord Compression

Spinal Cord Compression (SCC) is one of the most feared complications of cancer. It is a complication seen in approximately 5% of all cancer patients. Vertebral metastases occur in 3-5% of all cancers; It is more common in patients with breast, prostate, lung cancer, multiple myeloma, lymphomas, melanoma, renal tumors, and cancers of unknown origin. The most common involvement is in the thoracic region, the lumbosacral region is the second, and the cervical region is the third

(46). Initially, in 90% of cases, there is a pain in the localized area. Later, weakness in the legs, gait disturbance, and numbness in the fingers begin. Motor and sensory loss, autonomic dysfunction, Urinary retention, or incontinence may be seen. Treatment should be initiated without delay in all patients with suspected SCC, preferably after imaging studies have been performed to help preserve neurological function (47,48). Radiation therapy sustains the cornerstone of the treatment for most patients with SCC (49). Corticosteroids are effective by reducing vasogenic edema and lysis of susceptible tumors. They also reduce edema due to radiotherapy. Surgical methods can be applied in cases where the spine's integrity is impaired and previously unsuccessful radiotherapy.

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