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Drug Induced Hematological Disorders

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Drug Induced Hematological Disorders

- Thrombocytopenia
- Thromboembolic diseases
- Neutropenia and Agranulocytosis
- Anemia

Thrombocytopenia
-Definition

- The normal range for platelet counts usually is 150,000-400,000 /µl.
- Thrombocytopenia is defined as a platelet count below 150,000/µl or a 50% decrease in the platelet count from baseline.

Common Causative agents

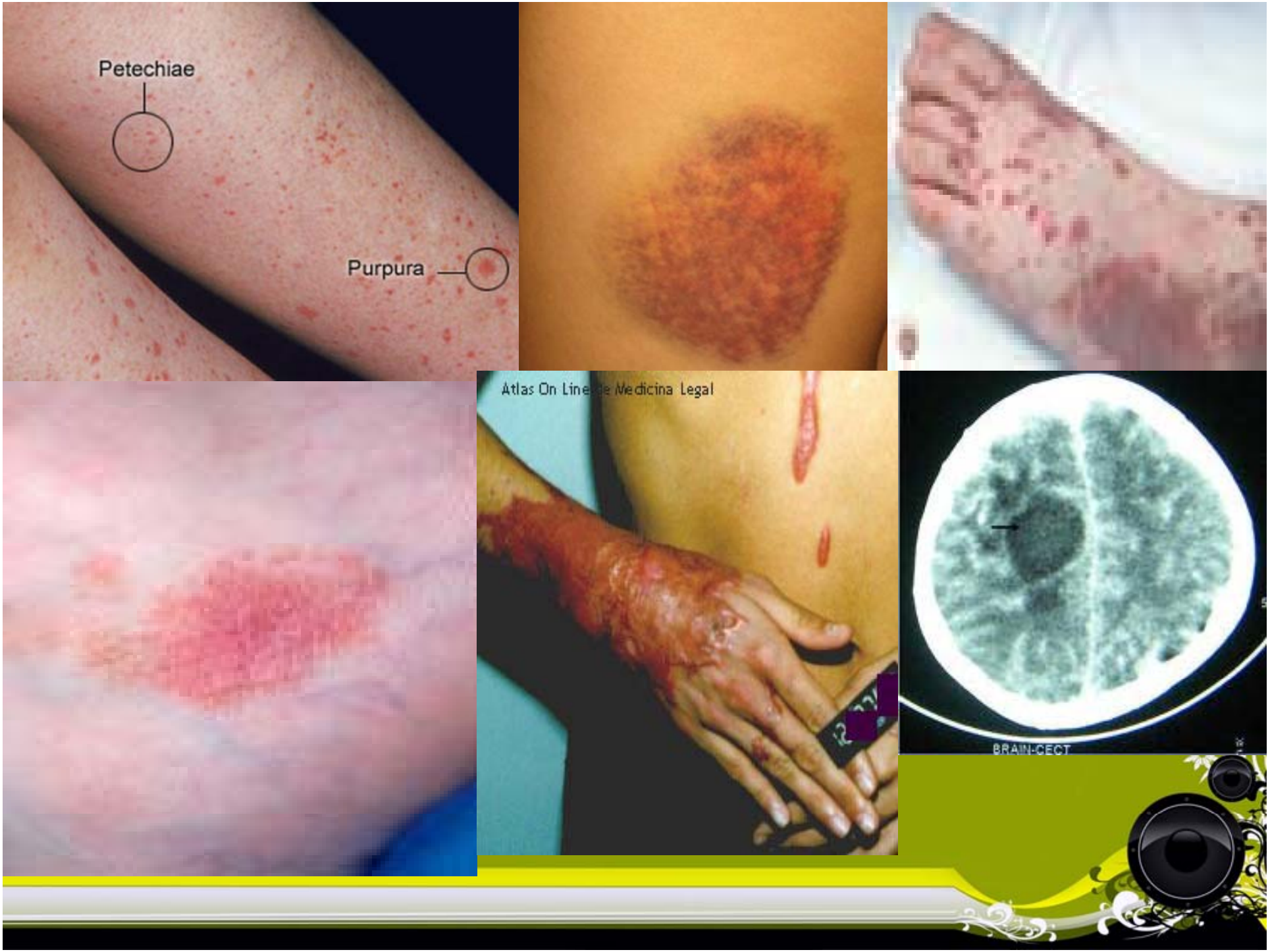
- Cancer chemotherapy agents
- Heparin
- Quinidine
- Quinine
- Gold salts
- Valproic acid
- Sirolimus
- Sulfa antibiotics

Clinical presentation

- Signs and symptoms usually occur when the platelet count falls below 100,000/µL,
  - Minor bleeding (petechiae, ecchymosis, gingival bleeding, microscopic hematuria, and epistaxis)
  - Significant bleeding (retroperitoneal, CNS, GI) occur when platelet counts decline to below 50,000/µL.
  - The median onset of thrombocytopenia is approximately 14 days, with a range of 1 day to 3 years.

Differential DX

- thrombosis does not occur in patients with drug-induced thrombocytopenia, except in association with heparin, a fact that may help to distinguish thrombocytopenia induced by drugs from that caused by other etiologies.


Petechiae
Purpura
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BRAIN-CECT

Heparin is associated with two types of thrombocytopenia

- HIT (Heparin Induced Thrombocytopenia)
- Type I HIT (HAT): Generally is mild and platelet counts rarely fall below 100,000/ µL. Usually occurs within 48-72 hours of initiation of heparin therapy and platelet counts normalize within a few days after discontinuation of heparin. The risk of thrombosis is extremely low.
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- Type II HIT: Usually occurs after 5-7 days following first exposure to heparin and more rapidly on second exposure. Platelet counts decline to below 100,000/µL. In patients with Type II HIT, a major clinical manifestation is the occurrence of thrombosis.

Risk factors for drug induced thrombocytopenia

Drug	Risk factor
Heparin	Prior exposure to heparin, especially within 100 days before current heparin treatment
Low molecular weight heparins	Prior exposure to low molecular weight heparins
Valproic acid	Advancing age(age>60-65 years), concurrent use of aspirin, high serum valproic acid concentrations (daily doses>1000 mg)
Sirolimus	Through blood concentrations>16ng/ml
Myelosuppresive chemotherapy drugs	Prior therapy with Myelosuppresive chemotherapy drugs, prior bone marrow transplantation

Drug induced thrombocytopenia incidence

Drug		Incidence reported
Sirolimus		13-30%
Heparin		1-30%
Valproic acid		9%
Low molecular weight heparins		1-3%
Cancer chemotherapy drugs	Gemtuzumab	99%
	Interferon-α2a	22-70%
	Carboplatin	37-80%
	Etoposide	41%

Morbidity and mortality

- The major morbidity: bleeding.
- Mortality risk is relatively low, however, the risk of serious and potentially life threatening bleeding is not negligible.
- Death may occur in patients with HIT, most commonly as a result of stroke or pulmonary embolism.

Management

- Withdraw suspected causative agent
- Platelet transfusions
- Prednisolone
- IVIG
- Methylprednisolone

Thromboembolic Diseases
-Definition

- is a collective term for thrombotic and embolic disorders.
- Thrombotic disorders are characterized by the formation of a clot produced from blood that attach to the vessel or heart wall causing an incomplete occlusion. When complete occlusion occurs, the clot is then called an embolism.
- Venus thromboembolism (VTE) is a common thromboembolic disorder, which may present as a deep vein thrombosis(DVT) means clot is in the leg or groin, or a pulmonary embolism (PE) that clot lodged in a vessel of lung.

Causative agents

- Hematopoetic agents (Erythropoietin), Goserelin, Tamoxifen, Antineoplastics (Cisplatin, Paclitaxel, Estramustine),
- Immunologic agents (Basiliximab, Foscarnet, Interfron alfa 2b, Sirolimus), Clozapine, Celecoxib, Anastrazole

Clinical presentation and differential diagnosis

- The signs and symptoms of VTE vary depending on the length of time between the development of a DVT or PE and the presentation.
- Drug induced thromboembolic disease does not differ in appearance from non-drug induced disease.

Symptoms associated with drug-induced VTE

DVT: A clot in the vessels of the leg or groin

- Unilateral warmth, redness or swelling
- Skin discoloration (ie, pallor, cyanosis, or erythema)
- Pain or tenderness
- Palpation of a nickel-size obstruction

PE: A clot in the vessels of the lung

- Isolated dyspnea
- Pleuritic pain
- Hemoptysis
- Syncope
- Cough

Risk factors for drug induced thromboembolic events

Independent acquired risk factors	Dependent acquired risk factors	Hereditary risk factors
Recent surgery or cardiovascular interventions	Obesity	Factor XII deficiency
Advancing age	Smoking	Antithrombin deficiency
Recent trauma	CHF or cardiac disease	Protein C deficiency
Prolonged periods of immobilization	Lupus	Protein S deficiency
Malignant neoplasms	Nephrotic syndrome	Excessive plasminogen activator inhibitor
Presence of central venous catheters or transvenous pacemakers	IBS	Prothrombin gene mutation
Liver disease	Myeloproliferative disorders	HIT
pregnancy		

Morbidity and mortality

- Significant morbidity and mortality.
- In the USA, PE is associated with a 30% mortality rate. Death has occurred within 1 hour to 30 days.
- Although Oral Contraceptives are the most well-known culprit of drug-induced VTE, mortality statistics are not available.

Management

- Treatment goals are to prevent death from PE, lyse the thromboembolism, relive associated symptoms, and prevent recurrence.

Information for patients

- Patients should be instructed to contact their primary care provider if symptom occur and to decrease preventable risk factors such as smoking and obesity.

Neutropenia and Agranulocytosis

Definition

- Neutropenia is defined as an absolute neutrophil count (ANC) less than 500 cells/mm^3
- Aranulocytosis, the concentration of granulocytes (a major class of WBC that includes N, B, E) drops below 100 cells/mm^3 of blood, which is less than 5% of the normal value

Causative agents

- Antineoplastic agents (Cisplatin, Gemcitabine, Capecitabine, Cytarabine, Doxorubicin, Vinorelbine, Cyclophosphamide, Ifosfamide Carboplatin, Methotrexate, Bleomycin),
- NSAIDs (Sulfasalazine),
- anti-thyroid (Methimazole, Propylthiouracil), cardiovascular drugs (Ticlopidine) and antipsychotic agents (Clozapine).

Clinical presentation

- Patients with an ANC less than 500/mm^3 are at risk for bacteremia from either the bowel or skin flora.
- The typical time course for onset of drug-induced agranulocytosis is 7-14 days.
- After discontinuing the suspected agent, bone marrow recovery can be expected within 10-14 days.

Signs and symptoms

- Bronchitis
- Fever
- Gingivitis
- Pharyngitis
- Sepsis
- Sore throat
- Sinusitis
- Stomatitis

Risk factors for drug- induced neutropenia

- Advancing age
- Autoimmune disease
- Female sex
- Genetic predisposition
- Mononucleosis
- Renal insufficiency
- Multi-agent chemotherapy regimens

Great hints…

- Case reports suggest that the use of particular drugs in specific disease states, such as the use of captopril in renal failure, and the use of specific drug combinations, such as captopril with probenecid or interferon, may increase the risk of agranulocytosis.
- Genetic predisposition to agranulocytosis may be induced by drugs such as methimazole or clozapine.

Morbidity and mortality

- Approximately one-half of neutropenic patients who become febrile have an established or occult infection.
- The risk increases even more when the ANC falls below $100/mm^3$, also known as severe neutropenia, in which 20% of febrile patients develop an associated bacteremia.
- The mortality can decrease with improved antibacterial therapy and prompt recognition by clinicians.

Management

Neutropenia associated with chemotherapy drug regimens

- Broad-spectrum antibiotics
- Dose reduction
- Discontinue the most myelosuppressive agent
- Change to a less myelosuppressive regimen
- Filgrastim or sargomostim for subsequent cycles of chemotherapy

Neutropenia associated with non-cytotoxic drugs

- Discontinue
- Filgrastim or sargomostim to accelerate neutrophil recovery
- Broad-spectrum antibiotics

Information for patients

- Patients undergoing cytotoxic chemotherapy should be counseled regarding the symptoms associated with the drug-induced disease .

Anemia(all types)
-Definition

- Reduction below normal in Hct or the concentration of Hgb or RBC
- Hgb is preferred parameter because of its accuracy and reproducibility.
- The NL serum Hgb ranges varies with age, sex and altitude of residence; the normal ranges are 12.3-15.3 g/dL for women and 14-17.4 g/dL for men.

Causative agents

- Cancer chemotherapy agents (such as alkylating agents, antimetabolites and antimitotics),
- Carbamazepine,
- Felbamate,
- Gold salts,
- Chloramphenicol,
- Linezolid,
- NSAIDs.

Clinical presentation and

- Aplastic anemia takes 1 month of drug therapy to develop but drug-induced hemolytic anemia may present as long as several weeks after therapy is initiated.

General:

- Weakness, Lethargy, Fatigue, Headache, Tachycardia

Aplastic anemia:

- symptoms above and also signs and symptoms of neutropenia and thrombocytopenia

Differential DX

- Before attributing an anemia to a drug, the clinician must first rule out other common causes of anemia, such as iron, B12, or folic acid deficiency, and acute or chronic blood loss.

Risk factors for drug- induced anemias

Iron deficiency anemia

Patient factors that predispose for GI bleeding:

- Ulcers
- Advanced age
- Multiple NSAIDs
- Cancer
- Ulcerative colitis

Hemolytic anemia

Rare inherited disorders:

- G6PD deficiency
- Thalassemias
- Sickle cell anemia
- Valve replacement
- Graft rejection
- Infections, particularly in those with hereditary disorders

Aplastic anemia

- Exposure to pesticides and chemicals
- Viral exposure (hepatitis A)
- Occupational radiation exposure

Morbidity and Mortality

- In an analysis of fatal adverse drug reactions, drug induced hematologic disorders were the most frequent cause of death.
- Mortality rates associated with aplastic anemia and hemolytic anemia are 51% and 4% respectively.
- Drug that suppress the bone marrow, including chemotherapy and zidovudine, cause clinically significant morbidity and mortality.
- The most clear prevention strategy for hemolytic anemia is to genetically test patients for G6PD deficiency.
- Patients at risk for drug- induced aplastic anemia can undergo periodic monitoring of serum hemoglobin concentration and hematocrit.

Management

- Discontinuation of the drug usually results in resolution of the anemia.
- Severe and acute cases: transfusion
- Epoetin therapy, iron supplementation , B12 supplementation , folic supplementation, immunosuppression , and androgens depend on the types of anemia could be the choice remedy.

Information for patients

- For NSAIDs and other drugs known to cause GI bleeding, patients should be advised to monitor stools for evidence of bleeding.
- Patient with G6PD deficiency, should be educated on the causes and for signs and symptoms of bleeding.
- Patients receiving drugs associated with anemia should be advised regarding the usual signs and symptom of anemia: fatigue, shortness of breath and pallor.
- For specific drugs where routine monitoring of the CBC is recommended, patients should be advised for required visits and monitoring.
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