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SPLENOMEGALY INDUCED BY DRUGS

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SUMMARY

The diagnosis of drug-induced splenomegaly is based on exposure to chemicals shortly before the spleen grows. The objective of this work is to review studies in the literature related to drugs and other substances that can directly or indirectly cause splenomegaly. Such drugs may have a direct effect on the spleen or cause it to enlarge as a result of disturbances in other organs, mainly the liver and the hemato-immune system. Some substances induce hemolysis, while others cause venous congestion, due to portal occlusion, of pre-hepatic, hepatic or post-hepatic origin. Most of the splenic side effects of these drugs are transient and discontinued, with the spleen returning to its original size after stopping the medication. This topic is complex and needs to be well understood, them properly.

SUMMARY

DRUG - INDUCED SPLENOMEGALY

The diagnosis of splenomegaly due to drugs is based on a recent history of exposure to a drug before the spleen enlargement. The purpose of this paper is to review studies of the literature on drugs that may induce splenomegaly. Drugs may provoke the enlargement of spleen by direct effect in splenic cells or as a side effect of disturbances in other organs, mainly liver and haematoimmunologic system. Some drugs provoke severe haemolysis associated with splenomegaly. Another cause of spleen increasing in size is the venous congestion due to liver disturbance with portal vein occlusion. All these drug side effects are usually transient and splenomegaly disappears when the medication is discontinued. This is a complex problem that must be better studied to be understood in order to prevent its occurrence and to find the best treatment.

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INTRODUCTION

All drugs interfere with the metabolism and function of organs and systems. Generally, this influence is not detected morphologically or by routine complementary exams. When drugs are used for a short period, their effects are transient, but they can become chronic when continuous or repeated use persists.

Even after thousands of studies over the past 20 years, the spleen remains a *organ full of mysteries* (as Galen already wrote), with most of its functions still not clearly understood[1]. The spleen is capable of increasing its dimensions more than all other organs. When normal, its length does not exceed 12 cm and its weight is around 200 g. However, in the presence of hematological, metabolic or venous obstructive disorders, the spleen can reach more than 50 cm in length and weigh more than seven kilograms.

Splenomegaly should be considered different from hypersplenism. Hypersplenism is a very rare condition, associated with splenomegaly, pancytopenia and bone marrow hyperfunction to compensate for the drop in blood element values. Its diagnosis is completed with the normalization of this condition after complete removal of the spleen.[two]. On the other hand, there are a wide variety of causes that provoke splenomegaly. These disorders can be divided into six categories[3-10]:

- splenic hypertrophy resulting from an immune response to sepsis;
- erythrocyte destruction, causing splenic hypertrophy, by increasing its function or by erythrocyte disorders;
- congestion due to difficulty in venous drainage from the spleen;
- Infiltration of elements produced by metabolic disorders;
- splenic and hematological cancer;
- other splenic and systemic causes.

Many authors confuse the term splenic sequestration with storage by the spleen. Splenic storage is a physiological condition of this organ, through which the spleen keeps normal blood elements inside, such as red blood cells, leukocytes, platelets, immunoglobulins, complement factors and other opsonins, which are released into the circulation in case of need. . In these patients, circulating pancytopenia is not clinically accompanied, even with very low hematological values. In splenic sequestration, normal blood elements are maintained or destroyed by the spleen, which does not release them if necessary.[two].

Drugs interfere with the function of all organs, including those of the spleen. Because there is no specific test for spleen functions, it is difficult to establish the relationship between drugs and splenic disorders.

Drugs that Act Directly on Spleen Size

Granulocyte macrophage-colony stimulating factor (GM-CSF) is one of the most commonly used growth factors to enhance the immune response and is known to recruit and activate antigen-presenting factors. One of its effects is to stimulate the proliferation of macrophages and consequently increase splenic and hepatic dimensions.[11-14].

Recombinant human granulocyte colony-stimulating factor (rhG-CSF) is an effective substance in the treatment of patients with hematological disorders, mainly in patients with leukemia scheduled for bone marrow transplantation. Daily injection of this drug causes massive splenic leukocytosis and hematopoiesis in addition to spleen growth. rhG-CSF increases the number of granulocytes in the red pulp and the number of circulating neutrophils. This drug not only reduces neutropenia and neutrophilic dysfunction, but also improves the function of these cells. It also induces increased cellularity in the bone marrow. The expression levels of TS and TKmRNAs (TS mRNA/ß-actin m RNAand TK mRNA//ßactin m RNA respectively) in spleen and bone marrow cells are also elevated[11-14].

Splenomegaly resulting from the action of rhG-CSF does not require treatment, as it causes little discomfort and can be transient.[11-18]. However, splenic rupture resulting from the abrupt growth of the spleen has already been reported in the literature.

Another drug that can stimulate splenocytes is rifampicin. This finding, with no adverse effect detected, has not yet been explained and its mechanism is not known.[19].

Methylene blue trihydrate is used as a dye and therapeutic agent for methemoglobinemia and oxidative damage to red blood cells. It is also useful for detecting digestive fistulas and urinary tract lesions. In addition to these effects, methylene blue causes hematopoiesis and congestion of the spleen and liver, with consequent splenomegaly, as well as bone marrow hyperplasia.[20].

Benzo(a)pyrene (BaP) is an immunomodulator consisting of a polycyclic aromatic hydrocarbon. In high doses, it is immunosuppressive, but in low concentrations it improves the immune response. As an associated effect, it reduces the number of erythrocytes and increases the size of the spleen at the expense of erythroid elements left over from intense splenic hemolysis and hematopoiesis.[21.22].

Splenomegaly was also found after using

of some anesthetic drugs, such as barbiturates, thiopental, acepromazine, butorphanol and ketamine. This increase results from erythrocyte congestion of the spleen and relaxation of the smooth muscles of its capsule by a still unknown mechanism. Other drugs such as medetomidine and benzodiazepines are associated with the growth of this organ.[23,24].

Graft disease inhibitors *versus* host - *graft versus host* (GVH) -, such as aurofin, azathioprine and methotrexate, have splenomegaly as side effects. Serotonin and histamine antagonists, mainly piroxicam, amitriptyline and cyproheptadine are GVH suppressors and cause splenomegaly. However, the mechanism of this phenomenon has not yet been established.[25].

On the other hand, there are drugs that act in the opposite way, that is, they reduce splenic dimensions. Among these drugs are cocaine, heroin and morphine, which constrict the splenic capsule and decrease the proliferation of splenocytes, thus reducing the size and weight of the spleen.

Splenomegaly Due to Drugs that Induce Hemolysis

Erythrocytes can be damaged by trauma, antibodies, drugs, organic functional disorders and toxins. Immune hemolysis is based on red blood cells bound to immunoglobulins (IgG, IgM and IgA) and aggregated to macrophages and monocytes, which contain receptors for immunoglobulin molecules (FcRI, FcRII and FcRIII). Macrophage digestion of part of the erythrocyte membrane destroys a considerable area of its surface. Damaged erythrocytes are taken up by the mononuclear phagocytic system, particularly the spleen. This extravascular hemolysis results in the release of large amounts of erythrocyte corpuscles, which are stored in the red pulp of the spleen and contribute to the enlargement of this organ.[28].

Drug-induced hemolysis is a rare condition, still controversial as to its real existence and indistinguishable from autoimmune hemolytic anemia[29]. There are more than a hundred drugs, such as penicillins, quinidine, phenacetin and cephalosporins, which have been identified in the pathogenesis of hemolytic anemia. Quinidine and phenacetin bind to antibodies and these immune complexes can adhere to the red blood cell membrane causing intravascular hemolysis.[30]. The hemolytic mechanism of penicillins and cephalosporins includes the union of these antibiotics with the erythrocyte membrane to form immune complexes and generate an immune response, with the formation of IgG and antibodies against red blood cells. When the administration of these antibiotics is stopped, these effects disappear in a short period of time.[22, 31, 32].

Other drugs such as alpha-methyldopa, levodopa and non-steroidal anti-inflammatory drugs (ibuprofen, mafanamic acid, diclofenac sodium, naproxen, acetyl salicylic acid, etc.), in addition to fludarabine, carboplatin, beta-lactamase and procainamide, can alter a membrane antigen and stimulate the production of immunoglobulins, mainly IgG, which cross-reacts with the antigen. Its mechanism of hemolysis is similar to that found in autoimmune hemolytic anemia. The growth of the spleen is due to the expansion of its lymphoid elements and erythroid elements of this organ.[22, 31, 32].

Oxidative attack is another mechanism of drug-induced hemolysis. Hydroxylated metabolites of aniline and dapsone (4-4'-diaminodiphenylsulfone, phenylhydroxylamine and dapsone hydroxylamine) induce iron release and methaemoglobin formation. Dapsone, sulfasalazine, phenacetin, sodium perchlorate, nitroglycerin, phenazopyridine, primaquine, and vitamin K analogues can be inserted into hemoglobin, hindering its oxidation. In this way, superoxide, hydroxyl and peroxide free radicals are generated. Hemoglobin is oxidized to form Heinz bodies, sulphahemoglobin, and methemoglobin. The presence of sulfur in the heme ring reduces oxygen transport. As a result of this reaction and due to hemolysis of senile red blood cells, the amount of free iron in the spleen increases, increasing the weight of this organ.[22,23].

Hydroxyurea is used in patients with sickle cell anemia to reduce its severity. However, this drug can cause symptomatic splenomegaly. The pain resulting from this increase can be very intense and be an indication for complete removal of this organ, with a consequent asplenic state.[34].

Another cause of splenomegaly is exposure to cadmium (CdCl). Histopathological examination of the spleen reveals deposits of iron and lipids in the lymphatics of the periarterial layer. The red pulp also expands and there is erythrocyte destruction by cadmium.[35].

Other drugs such as quinine and clopidogrel are responsible for immune thrombocytopenia and hemolytic anemia.[36].

Snake venom toxins, clostridial lecithinases, *M. pneumoniae*, *H. influenzae* or plasmodia, in addition to other parasites, are the cause of splenomegaly, but their study is not the purpose of this publication.

Splenomegaly Due to Drugs Affecting the Liver

Drugs and toxins are responsible for less than 5% of cases of jaundice, hepatitis and other liver disorders, but when they occur, they cause severe hepatobiliary disorders[22,37]. The diagnosis of liver alteration caused by drugs is circumstantial and becomes unequivocal only if there are no other factors that may be involved in the liver disease.[38,39].

Hepatotoxic drug reactions can be divided

between predictable and idiosyncratic. The predictable ones are, in general, dose-dependent and associated with drugs whose metabolism is related to the formation of hepatotoxic substances. The idiosyncratic mechanisms are dose-independent and, although they do not form hepatotoxic metabolites, immune responses to drug components may arise. Hepatotoxicity can be evidenced by chronic active hepatitis, hepatic steatosis, phospholipidosis, granulomatosis, hepatic vascular lesions, non-cirrhotic portal hypertension, cirrhosis, and even benign or malignant neoplasms[39-42].

Hepatocyte functional disorders are the most common side effects of most drugs. Antibiotics are the drugs most related to liver disorders. Macrolides (roxithromycin and claritoromycin), isoniazid, rifampicin, amoxicillin, minocycline, nitrofurantoin, flucloxacillin and clavulinic acid are antibiotics frequently involved in liver disease. Other drugs such as thiamazole, pyrazinamide, satolol, pravastatin, zidovudine, quinidine, ritonavir, cotrimoxazole, ranitidine, propylthiouracil, methimazole, methyldopamine can also cause acute hepatitis[37,39,40,43-45]. Chemotherapeutics, such as 6-thioguanine and 6-mercaptopurine, used in the treatment of leukemias, can cause veno-occlusive diseases, with consequent portal hypertension, accompanied by splenomegaly and the formation of extensive varicose veins[37, 40, 46].

Another mechanism of liver disorder is obstruction to biliary drainage with consequent cholestasis. Anesthetics, especially halothane, anticonvulsants and other drugs (enalapril, erythromycin, troleandomycin, estrogens, chlorpromazine, sulfonamides, fluvastin, mesalazine, thienyl acid and dihydralazine) are among the most mentioned as responsible for cholestasis, either by ductal destruction or by of interstitial hepatitis[38.39].

Illicit drugs, especially marijuana and *crack*, play a hepatotoxic role, and this effect is exacerbated by alcoholism. Chronic liver conditions are accompanied by portal hypertension and enlarged spleen[47].

Drug-induced liver disease is generally of low intensity, but in some cases it may present with jaundice, steatosis, veno-occlusive disorders and portal hypertension due to intrahepatic venous stasis. In most of these cases, venous stasis spreads throughout the portal territory and splenomegaly occurs. Therefore, splenomegaly is not due to splenic affection or drug action in this organ, but as a side effect of the liver disorder. Complementary exams may indicate pancytopenia, but it does not reflect hypersplenism and there is no clinical manifestation that indicates splenic or hematological disease, despite vascular congestion of the spleen.

An enlarged spleen may be the first or most obvious sign of drug-induced liver disease.

Splenomegaly in metabolic diseases, such as dyslipidemias (Gaucher's, Niemann-Pick's, Faber's diseases, etc.) and in hematological disorders (myeloid hepatosplenomegaly, lymphomas, leukemias, etc.) is well known[5,7,9]. Growth of this organ also occurs in congestive heart failure and chronic liver disease due to venous stasis. In general, in all these conditions, the splenic functions are preserved, despite the intense respiratory, abdominal and walking discomfort, proportional to the dimensions of the organ.

Splenomegaly due to various causes

To avoid these adversities, splenectomy has been progressively less indicated and when surgery on the spleen is unavoidable, the trend has been towards conservative procedures, including partial splenectomy, subtotal splenectomy and autogenous implants of splenic tissue. These operations remove benign splenic diseases located in only one part of the spleen (hemangiomas, cysts, granulomas, etc.), in addition to allowing splenoreduction, with consequent relief of symptoms caused by splenomegaly[5,10,47-52]. Cytopenia, which can occur as a side effect of some drugs, is not mediated by the spleen or its functions[two]. This cytopenia is only a laboratory finding, without clinical manifestation.

The spleen is capable of increasing more than 20 times its size, usually slowly and almost imperceptibly until it reaches large dimensions. Malpighi's capsule is very thin and does not support rapid distension of the splenic parenchyma, breaking and causing profuse hemorrhage. Drugs, such as rhG-CSF, can cause sudden splenomegaly, with consequent organ rupture. This occurrence is known in leukemias[9].

In most cases, the treatment of splenic rupture can be conservative, with the patient hospitalized and under continuous observation, for at least two weeks. Clinical study of the state of consciousness, heart rate, blood pressure and appearance of the mucous membranes are fundamental. When necessary, blood count and imaging exam (ultrasound or tomography) complement the patient's evaluation[2,8,11,12,14-18].

If there is instability of consciousness or hemodynamics, or if the patient develops an acute abdomen, laparotomy is mandatory. In this situation, the splenic lesions are identified and the best operation is chosen, with a view to preserving at least part of the organ (splenorrhaphy, selective vascular ligation, partial splenectomy, subtotal splenectomy or total splenectomy complemented by autogenous implants of splenic tissue over the omentum). bigger)[51.52].

There are reports in the literature that illicit drugs, such as heroin, morphine and cocaine, cause contraction

of the splenic capsule, with a consequent increase in the levels of blood elements. Cocaine is also a potent vasoconstrictor, an effect that contributes to splenoreduction. Extensive splenic infarcts are not uncommon in cocaine users. Noradrenaline is another drug associated with splenic constriction. It is even believed that catecholamines are mediators responsible for splenic shrinkage after the use of opioids. In this situation, erythrocythemia and increased hemoglobin occur, with a consequent increase in cellular oxygenation.[26,27].

Splenic pain is another rare complication that can be provoked by drugs. This symptom results from sudden distension of the splenic capsule or vascular obstruction, with consequent ischemia of the organ. In both situations, the pain is transient and disappears after discontinuing the medication that caused it. Exceptionally, the pain persists even without the use of the drug and is refractory to common analgesics. This condition, whose pathophysiology is still unknown, when very intense and disabling, may indicate the removal of the ischemic part of the spleen. If the entire spleen is diseased, it can be completely removed and autogenous implants of splenic tissue will be sutured to the greater omentum to maintain the functions of this organ and prevent the asplenic state.[53-56].

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