

Alveolar haemorrhage syndrome – a rare side effect during some frequently used therapies

*Sindromul de hemoragie alveolară – un efect advers rar
în cursul unor terapii frecvente*

Abstract

Alveolar haemorrhage syndrome is a serious condition with deadly potential and with a variety of etiology: autoimmune diseases associated with vasculitis, infectious, idiopathic, drug-induced or following exposure to toxic substances, in the context of cardiac disease, coagulation disorders or secondary to bone marrow transplant or organ transplant. Clinically, it manifests with dyspnea, fever, cough and haemoptysis, the paraclinical manifestations being acute hypoxemic respiratory failure, anemic and radiological syndrome with the occurrence of diffuse pulmonary infiltrate. The diagnosis remains one of exclusion, requiring a series of additional tests depending on the etiological suspicion. The confirmation is obtained by bronchoscopy with bronchoalveolar lavage, a haemorrhagic lavage fluid with increased erythrocyte content being the sign of alveolar haemorrhage, and the severity of bleeding is assessed by the Golde score. If the etiology is uncertain, the pulmonary biopsy is indicated. The treatment is based on etiology, especially in case of drug etiology, and can be conservative, supportive, with discontinuation of the incriminated drug. Corticoids and immunosuppressants are administered, especially when vasculitis phenomena are associated. Considering the severity of clinical manifestations and their consequences, alveolar haemorrhage syndrome is always a diagnostic and therapeutic emergency irrespective of the mechanism of production. This article reviews the various medications commonly used in medical practice which may have an alveolar haemorrhage syndrome as adverse reaction, produced by various mechanisms.

Keywords: alveolar haemorrhage, drug, pulmonary toxicity

Rezumat

Sindromul de hemoragie alveolară este o afecțiune gravă cu potențial fatal, cu etiologie variată: imună/autoimună asociată cu vasculită/capilarită, infecțioasă, idiopatică, indusă medicamentos sau prin expunere la toxice, în contextul bolilor cardiace, al tulburărilor de coagulare sau secundară transplantului de măduvă osoasă sau de organe. Se manifestă clinic prin dispnee, febră, tuse și hemoptizii, paraclinic cu insuficiență respiratorie acută hipoxemică, sindrom anemic și radiologic, cu apariția de infiltrate pulmonare difuze bilaterale. Diagnosticul rămâne unul de excludere, necesitând o serie de teste suplimentare în funcție de suspiciunea etiologică. Confirmarea hemoragiei alveolare se face prin bronhoscopie cu lavaj bronhoalveolar, cu evidențierea unui lichid de lavaj hemoragic cu conținut crescut de eritrocyte, iar severitatea hemoragiei este apreciată cu ajutorul scorului Golde. Dacă etiologia este incertă, se indică biopsia pulmonară. Tratamentul se face în funcție de etiologie – în special în cazul celei medicamentoase – și poate fi conservator, suportiv, prin întreruperea medicamentului incriminat. Se administrează corticoizi și imunosupresoare, mai ales când există fenomene de vasculită asociate. Ținând cont de severitatea manifestărilor clinice și a consecințelor sale, sindromul hemoragic alveolar este întotdeauna o urgență diagnostică și terapeutică, indiferent de mecanismul de producere. Articolul trece în revistă diferitele medicamente folosite frecvent în practica medicală ce pot avea ca reacție adversă sindromul hemoragic alveolar, produs prin diferite mecanisme.

Cuvinte-cheie: hemoragie alveolară, medicament, toxicitate pulmonară

Alina Valentina Dobrota¹,
Aneta Șerbescu²,
Alina Croitoru^{2,3},
Bianca Paraschiv⁴,
Alexandru Miron Bogdan^{2,3},
Claudia Toma^{2,3}

1. Floreasca Clinical Emergency Hospital, Bucharest

2. "Marius Nasta" Institute of Pneumophthysiology, Bucharest

3. "Carol Davila" University of Medicine and Pharmacy, Bucharest

4. "Sf. Ioan" Clinical Emergency Hospital, Bucharest

Corresponding author:
Alina Dobrota MD, PhD student
E-mail: alina.valentina.pirvu@gmail.com

Introduction

Alveolar haemorrhage syndrome is a serious, sometimes life-threatening condition, clinically manifested with coughing, dyspnea, fatigue, and haemoptysis. The syndrome may have many causes, including drug treatments. Due to the rarity of this type of adverse reaction to a drug, the etiological relationship between an incriminated drug and alveolar haemorrhagic syndrome is difficult to specify.

The alveolar haemorrhage syndrome

It is clinically manifested by dyspnea, coughing, fatigue, and sometimes haemoptysis. From a paraclinical point of view, the patient may present anemic syn-

drome, acute hypoxemic respiratory failure and radiologic diffuse bilateral lung infiltration. The diagnosis remains one of exclusion and is confirmed by bronchoscopy with bronchoalveolar lavage or pulmonary biopsy.

Diffuse alveolar haemorrhage results from damage to small lung vessels, leading to the collection of blood inside the lung alveoli, thus affecting alveolar-capillary gas exchanges. In theory, any source of lesion of alveolar microcirculation may cause alveolar haemorrhage. The pathophysiology and specific manifestations vary according to etiology, and the clinical characteristics of each patient's disease are determined by the place, size and type of the vessel involved.

Alveolar haemorrhage may have a variety of causes:

1. Autoimmune diseases – Wegener's granulomatosis, microscopic polyangiitis, Goodpasture syndrome, Henoch-Schonlein purpura, Churg-Strauss syndrome, connective tissue diseases, antiphospholipid syndrome, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, cryoglobulinemia etc.

2. Infectious – depending on immunological status in immunocompromised patients, the most frequent infections causing diffuse alveolar haemorrhage are those with cytomegalovirus and adenovirus, *Aspergillus*, *Mycoplasma*, *Legionella*, and *Strongyloides stercoralis*. In immunocompetent patients, diffuse alveolar haemorrhage is mainly produced by *Leptospirosis* and *Malaria* parasites, influenza A (H1N1) virus and *Staphylococcus aureus*^(1,2).

3. Idiopathic – idiopathic pulmonary hemosiderosis is a rare cause of diffuse alveolar haemorrhage, most commonly encountered in children, affecting their physical development, with a prevalence of 0.24-0.26 per million⁽³⁾. It has an unknown etiology and over time produces chronic lung infiltration, leading to pulmonary fibrosis. The diagnosis of idiopathic pulmonary hemosiderosis is one of exclusion.

4. Induced by drugs or exposure to toxic substances – the drugs that most commonly cause alveolar haemorrhage are: propylthiouracil, amiodarone, nitrofurantoin, methotrexate, bleomycin, infliximab etc.

5. Coagulation disorders caused by diseases or anti-coagulant and anti-platelet agents (warfarin, GP IIb / IIIa inhibitors).

6. Heart disease – ex.: mitral stenosis, chronic heart failure, pulmonary thromboembolism, pulmonary hypertension, pulmonary veno-occlusive disease.

7. Exposure to pesticides, isocyanates, cocaine can also cause alveolar haemorrhage.

8. Hematopoietic stem cell transplantation or solid organ transplantation.

9. Some neoplasms: angiosarcoma, metastatic renal carcinoma.

The severity of alveolar haemorrhage is calculated using the Golde score, which quantifies the amount of hemosiderin. In normal subjects, the score is between 4 and 25. Values of the Golde score between 100 and 300 are found in alveolar haemorrhages of average severity; values between 300 and 400 are found only in severe ones. If there are more than 90% Fe-positive alveolar macrophages (erythrophage), there is certainly a severe alveolar haemorrhagic syndrome⁽⁴⁾.

Drug-induced alveolar bleeding

Among the causes of alveolar haemorrhage, the ones that are drug-induced rarely occur and may raise major etiological diagnosis problems. In the case of drug-induced alveolar haemorrhage, for most of the patients the mechanism is unknown and the diagnosis is often difficult because the results of routine laboratory analyses are not useful and the radiological changes are not

specific to alveolar haemorrhage syndrome. Confirming the diagnosis of drug-induced lung disease is based on a high suspicion, a detailed medical history of drug use or chronic treatment, and clinical improvement at the pathogen discontinuation.

The alveolar haemorrhage diagnosis is based on physician's suspicion, combined with clinical, laboratory, radiological and pathological characteristics. The suspicion is raised when a patient accuses dyspnea, cough, fever and haemoptysis (but they can be absent in one third of cases), acute respiratory failure, biological with anemic syndrome and radiologically with diffuse bilateral lung infiltration. Bronchoscopy with bronchioalveolar lavage confirms the diagnosis of alveolar haemorrhage by the macroscopic appearance of the lavage fluid (progressively haemorrhagic aspect) and subsequently by highlighting macrophage loaded with hemosiderin (erythrophage).

Also, a differential diagnosis with a wide range of diseases (autoimmune, cardiac, infectious, idiopathic, clotting, exposure to toxic substances, drug reaction) is required by performing the following tests: blood count, coagulation tests, platelets count, serological tests (antinuclear antibodies, anti-dsDNA, anti-GBM, ANCA), echocardiography, spirometry, alveolar-capillary diffusion. If the etiology of alveolar haemorrhage remains uncertain, a lung biopsy is indicated to show a possible underlying pathology.

Repeated episodes of alveolar haemorrhage can cause in time collagen deposit in small airways, leading eventually to pulmonary fibrosis. Since alveolar haemorrhage is a disease that can rapidly evolve to exitus, rapid and effective therapeutic means are required. Identification of a drug as causative agent and its discontinuation may be the only treatment necessary to achieve remission in varying degrees.

In the treatment of drug-induced alveolar haemorrhage syndrome, discontinuation of the suspected drug is of first intention and subsequently, especially in patients with acute respiratory failure, corticosteroid treatment and immunosuppressive drugs with patient monitoring are administered. Adjuvant methods can also be added: oxygen therapy, bronchodilators, cessation of anticoagulant medication if necessary and in severe cases, oro-tracheal intubation with mechanical ventilation can be performed.

More than 600 drugs have been incriminated in pulmonary adverse reactions⁽⁵⁾ and their number is increasing as new therapeutic agents develop.

Diffuse alveolar haemorrhage following drug therapy is often addressed in medical literature, and cases have been reported in many types of therapies, some of which are very commonly used, such as anticoagulant and anti-platelet medication or cytostatic medication. It is important to know that such side effects may occur, with a fatal outcome if not recognized and diagnosed in good time.

Several types of drug therapies that may induce alveolar haemorrhage are reviewed in the following.

Cancer therapy

Adverse reactions, including alveolar haemorrhage syndrome, have been reported over time in the treatment of neoplasms with cyclophosphamide, carmustine, gemcitabine, pemetrexed, and vincristine. Targeted molecular therapies are rarely mentioned. Currently, targeted molecular therapy in combination with radiotherapy and chemotherapy can improve treatment outcomes especially in solid tumours. However, there are side effects. Oesophageal radiotherapy can cause frequent radiation pneumonia, but no case of diffuse alveolar haemorrhage has been reported until 2014⁽¹²⁾.

Gemcitabine is a cytostatic agent active on solid tumours used for the treatment of non-small-cell lung cancer (NSCLC) and pancreatic cancer. Although over the years some cases of pulmonary toxicity have been described during gemcitabine therapy, the first case of diffuse alveolar haemorrhage was reported only in 2001⁽¹¹⁾.

Erlotinib hydrochloride is a drug used for the treatment of non-small-cell lung cancer, pancreatic cancer and many other types of cancer. It is an inhibitor of the tyrosine kinase receptor, which acts on the epidermal growth factor receptor (EGFR). In 2014, the first case of alveolar haemorrhage in a patient with esophageal carcinoma in combination treatment with chemotherapy and erlotinib was published in the *International Journal of Clinical and Experimental Medicine*. The reported incidence of pulmonary injury by erlotinib is 0.8-1%, most of which is interstitial pneumonia⁽¹²⁾.

Dasatinib is an oral inhibitor of Bcr-Abl tyrosine kinase (it inhibits the Philadelphia chromosome) and a tyrosine kinase inhibitor approved for use as a first-line treatment in patients with chronic granulocytic leukemia (CML) and acute lymphoblastic leukemia with Philadelphia chromosome-positive (Ph+). There are reports of adverse effects such as bone marrow suppression, bleeding with different localizations (cerebral haemorrhage, lower endocranial bleeding and gastrointestinal bleeding), pleural effusion and interstitial pneumonia. However, in January 2017, a case of alveolar haemorrhage during dasatinib therapy was reported, with favourable clinical outcome after the administered drugs were stopped and pulse therapy with methylprednisolone was initiated⁽¹³⁾.

Anti-inflammatory and immunosuppressive therapy

Pulmonary diseases secondary to drug use can be a common diagnosis, but frequently missed. Therefore, a high index of clinical suspicion and familiarity with clinical syndromes associated with drug use are important in establishing the diagnosis. Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used drug classes, and there is often a tendency for abuse. NSAIDs are safe when used in the prescribed doses and duration. Side effects of NSAID use are relatively common and can affect almost any organ or system of the body. NSAIDs are known to cause pul-

monary toxicity, most common reactions being hypersensitivity and bronchospasm.

Ketorolac tromethamine is one of the non-steroidal anti-inflammatory drugs (NSAIDs) indicated in short cures for the treatment of moderately severe acute pain requiring opioid analgesia. In 2013, a case of diffuse alveolar haemorrhage secondary to ketorolac treatment was reported. The patient was treated conservatively with favourable clinical evolution, and after two weeks the full resolution of bilateral lung infiltrations was imagistically revealed⁽¹⁴⁾.

D-Penicillamine (D-PC) is an anti-inflammatory drug that has been used to treat Wilson's disease, rheumatoid arthritis (RA) and systemic sclerosis (SSC). Most common side effects are renal complications: proteinuria, membranous nephropathy, and glomerulonephritis. Rarely, the diffuse alveolar haemorrhage may also occur.

Leflunomide is an isoxazole derivate with anti-inflammatory and immunomodulatory properties used in rheumatoid arthritis therapy. Pulmonary toxicity during treatment with leflunomide was very rarely described (1 out of 10,000 patients treated per year)⁽¹⁵⁾. In February 2004, a report showed that several death cases occurred due to interstitial lung disease in patients who participated in a post-marketing surveillance study of leflunomide in Japan⁽¹⁵⁾. This report indicated that 80 out of 400,000 patients who previously received leflunomide worldwide developed pulmonary adverse reactions. Pulmonary lesions were: eosinophilic pneumonia, cryptogenic organizing pneumonia, and rarely diffuse alveolar haemorrhage.

Azathioprine (AZA) is an immunosuppressive drug used in rheumatoid arthritis, Crohn's disease, ulcerative colitis, and kidney transplants to prevent rejection. The most frequent adverse reaction is marrow suppression, especially in patients with the genetic polymorphisms of thiopurine methyltransferase. In 2007, a case of an elderly patient with severe myelotoxicity and diffuse alveolar haemorrhage syndrome secondary to azathioprine treatment was published, followed by genetic testing indicating homozygous polymorphism associated with the absence of TPMT activity⁽¹⁶⁾.

Sirolimus is a protein kinase responsible for T cell inhibition and B cell proliferation. It is used in the treatment of post-transplant patients, especially renal transplantation, but also in the treatment of lymphoangiomyomatosis. Sirolimus has pulmonary side effects and may cause cryptogenic organizing pneumonia, diffuse alveolar haemorrhage, lymphocytic pneumonitis, hypersensitivity pneumonitis, desquamating interstitial pneumonia and pulmonary alveolar proteinosis.

The diagnosis is based on the combination of clinical, radiological, histological and pathological elements. In 2012, a study was published on a range of neoplastic and non-neoplastic lesions in allograft recipients of current immunosuppressive therapies⁽¹⁷⁾. The study included 28 renal transplant patients who required pulmonary biopsy for respiratory symptoms. The histological charac-

teristics were correlated with clinical data, but also with the administration of immunosuppressive drugs. The incidence of neoplasia in pulmonary biopsy was 0.4%, the association with pulmonary parenchymal disease was 0.4% (9 cases) and in 0.2% of cases there were histological features indicating a localized infection process. In patients treated with sirolimus, the incidence of neoplasia was less frequent than in patients treated with other immunosuppressive combinations (12.5% vs. 58.3%, $p=0.03$)^(17,18). Pulmonary biopsies in 4 out of 5 patients with clinical suspected pulmonary toxicity secondary to sirolimus treatment revealed alveolar haemorrhage as the only histological finding or in combination with other models.

Biological therapy in autoimmune pathology

Rituximab is an anti-CD20 IgG1 monoclonal antibody that is used for the treatment of non-Hodgkin's CD20 positive lymphoma. The side effects of rituximab include fever, chills and tremor (during rituximab infusion). These side effects are generally transient and directly proportional to the size of the tumour. Minor respiratory adverse reactions have been reported in 38% of patients treated with rituximab in clinical trials, including cough, rhinitis, bronchospasm, dyspnoea and sinusitis⁽¹⁹⁾. In some cases, severe adverse reactions have been described, such as cryptogenic organizing pneumonia, diffuse interstitial pneumonitis and alveolar haemorrhage, some of them being fatal.

Infliximab is a chimeric monoclonal antibody, an inhibitor of tumour necrosis factor alpha (anti-TNF-alpha), being increasingly used in the treatment of Crohn's disease, with a good safety profile and mild-to-moderate side effects. Less often serious side effects occur, including infections, hepatitis B reactivation, tuberculosis reactivation, hepatosplenic T cell lymphoma (generally only when combined with 6-mercaptopurine), drug-induced lupus, central nervous system disorders, psoriasis, and vitiligo. Also, in 2010, diffuse alveolar haemorrhage (after infliximab infusion) was reported as a side effect in a patient with Crohn's disease⁽²⁰⁾. The mechanism by which infliximab can cause pulmonary injury remains unknown.

Etanercept is a drug that acts against the alpha tumour necrosis factor and is used in the treatment of a variety of autoimmune diseases, with a good safety profile. Adverse reactions include erythema, pruritus, pain and swelling at the site of injection, hypersensitivity phenomena ranging from rash to anaphylaxis, hepatic cytolysis, pancytopenia, Steven-Johnson syndrome and bacterial, viral, or fungal infections, lymphoma, and reactivation of latent or active tuberculosis⁽²¹⁾. Rarely, etanercept can cause lung complications such as fatal alveolar haemorrhage syndrome in patients with autoimmune diseases and should be suspected especially when the patient has dyspnea, haemoptysis, diffuse pulmonary infiltrates, negative bacteriological exams and decreased haemoglobin and haematocrit.

Antiarrhythmic therapy

Amiodarone is an antiarrhythmic drug commonly used to treat and prevent a range of atrial or ventricular arrhythmias. These include ventricular tachycardia (VT), ventricular fibrillation (VF) and broad complex tachycardia, as well as atrial fibrillation and paroxysmal supraventricular tachycardia. Common minor side effects include fatigue, trembling, nausea, and constipation. One of the major adverse reactions is pulmonary toxicity. Several types of lung disease may occur, including interstitial fibrosis, cryptogenic organizing pneumonia, acute respiratory distress syndrome, diffuse alveolar haemorrhage, pulmonary masses or nodules, and pleural effusion⁽²²⁾. Two mechanisms for pulmonary toxicity secondary to amiodarone treatment have been proposed: 1) a direct toxic reaction with the accumulation of cellular phospholipids resulting from lysosomal phospholipases inhibition, and/or 2) an immunological mechanism linked to the activation of CD8 T-cell lymphocytes. The incidence of pulmonary toxicity varies between 5 and 15% and is correlated with the dose (cumulative dose >400 mg/day), duration of treatment (minimum two months), advanced patient age, pre-existing lung disease, history of thoracic surgery or pulmonary angiography⁽²²⁾.

Antibiotic therapy

Antibiotics that can cause pulmonary toxicity are ampicillin, bleomycin, cotrimoxazole, penicillin, and nitrofurantoin. Among them, nitrofurantoin is most often cited in the medical literature as having the alveolar diffuse haemorrhage syndrome as a possible adverse reaction.

Nitrofurantoin, an antibacterial agent used primarily for the treatment of urinary tract infections, is one of the most common causes of drug-induced lung disease. Pulmonary toxicity may be more frequently acute, or chronic (in a 3 to 1 ratio). The mechanism of acute pulmonary reaction to nitrofurantoin is unknown and is not dose-dependent. Pulmonary damage to nitrofurantoin occurs especially in women (75%) due to its wide use in urinary infections and due to the fact that it does not produce microbial resistance to antibiotics⁽²⁴⁾. Nitrofurantoin treatment should be ceased in all cases. Corticotherapy is indicated in respiratory failure cases.

Anticonvulsant therapy

Valproic acid (VPA) is one of the most commonly used antiepileptic drugs for the treatment of focal and generalized epilepsies, absences and Lennox-Gastaut syndrome (LGS). VPA demonstrated a negative effect on both intrinsic and extrinsic coagulation systems and there is controversy over the clinical relevance of these haematological abnormalities. Over time, many coagulopathies due to valproic acid have been described, the most common being thrombocytopenia. In 2015, a third case of reversible alveolar haemorrhage due to valproic acid was described⁽²⁵⁾. Diffuse alveolar haemorrhage is one of the rarest complications of the valproic acid treat-

ment, most likely secondary to a combination of several haemostatic disorders and could be reversible upon cessation of treatment.

Therapy for hyperthyroidism

Propylthiouracil (PTU) is commonly used in the treatment of hyperthyroidism and can produce positive ANCA vasculitis. However, pulmonary and renal damage is rare. PTU-induced positive p-ANCA vasculitis was first reported in 1993 and the pathophysiology mechanism remains uncertain^(26,27). It can manifest by fever, arthralgia, cutaneous vasculitis, and less frequently with fast progressive glomerulonephritis and diffuse alveolar haemorrhage. The most common side effects are skin-related, such as eczema, hives, hair loss, and skin pigmentation, but nausea, vomiting, loss of taste, myalgia, arthralgia and headache may also occur. Severe adverse reactions have been as well reported during the treatment with propylthiouracil: hepatic cytolysis, agranulocytosis and thrombocytopenia with increased risk of bleeding in vital organs, especially during the first months of treatment.

Conclusions

Drugs can induce pulmonary toxicity in varying degrees, from simple lung infiltration to acute injury.

Pulmonary damage secondary to drug use can be suspected if the patient is treated with a susceptible drug and develops new respiratory signs and symptoms, which improve after the discontinuation of the suspected drug⁽⁵⁾. Drug-induced pulmonary haemorrhage is a rare complication. The production mechanisms of alveolar haemorrhage may be by direct drug toxicity (bleomycin, methotrexate, nitrofurantoin, amiodarone), by immunological reactions (nitrofurantoin, sulphonamide, penicillin, phenytoin and propylthiouracil) or both. Several drugs, such as penicillamine, amiodarone, cocaine, hydralazine, mitomycin C, nitrofurantoin, abciximab, MTX, carbamazepine and several anticoagulants, are recognized as alveolar haemorrhage inducing agents.

The diagnosis of alveolar haemorrhage as an adverse drug reaction is difficult because of the polymorphism of drug reactions, and due to the fact that patients already have other comorbidities for which they are being treated, so the new symptoms may be attributed to the exacerbation of one of the pre-existing conditions. This is why making a detailed anamnesis of patient's comorbidity and treatment is required. Generally, the nonrecognition of pulmonary damage secondary to drugs may induce morbidity and mortality, especially in alveolar haemorrhage, a potentially fatal condition requiring emergency therapy. ■

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