DRUG RELATED PLEURAL DISEASE

Charis MOSCHOS MD., Ioannis KALOMENIDIS MD
2nd Department of Pulmonary Medicine, Athens Medical School "Atticon" Hospital, Rimini 1, Haidari, Greece
e-mail: ikalom@med.uoa.gr

General Considerations

Drug-related pleural disease may occur as an isolated disorder, accompany parenchymal disease, or may appear in the context of generalized, even life-threatening, systemic reactions. Several commonly used drugs can affect the pleura. Pleural effusions represent the most common manifestation. Drugs may also cause pleural thickening with or without pleural effusion and in even fewer cases, pneumothorax or hemothorax. The underlying pathogenetic mechanisms though not absolutely clear, have been proposed to include: hypersensitivity reactions, oxidative stress of mesothelial cells, dose-dependent toxic effect, fluid retention and induction of chemical inflammation (1).

Patient Management

Information concerning the clinical presentation and the course of drug-induced pleural disorders is of limited scientific quality since, for the most part comes from case reports and case series. The relative scarcity and the clinical heterogeneity of pleural disease secondary to drug intake hampers a systemic approach that would help in setting diagnostic algorithms and making therapeutic decisions.
Attributing a pleural disorder to a specific drug intake may prove an extremely complicated task. Most often, the patient would complain for exertional dyspnea, cough or pleuritic chest pain. Constitutional symptoms i.e. malaise and weight loss may also be present. Symptoms may occur acutely after the first dose of a new medication or may appear years latter, though a latent time of weeks to months is the rule. Pleural fluid features vary greatly between different patients and are not indicative of the diagnosis. Then, how should a link between a disorder and a drug can be established? Initially, all other potential causes should be excluded. Existing literature reports on similar cases can be supportive. Resolution after drug withdrawal and reoccurrence after drug re-administration -if possible- are of fundamental importance. A useful tool in helping clinicians establish causal relationship and especially important for publication purposes is the Naranjo adverse drug reaction probability scale which is described in Table 1 (2).
When drug-induced pleural disease is suspected, treatment mainly consists in discontinuation of the drug in question, although in some cases it may be irreplaceable or more than one drug may be implicated. Discontinuation of the drug is usually sufficient while sometimes corticosteroids are administered either because a hypersensitivity reaction is suspected or with intent to reduce pleural inflammation. With a few exceptions however, there are no sufficient data to prove corticosteroid efficiency. Pleural fluid drainage to releive dyspena may be sometimes required.

Cardiovascular Agents

Minoxidil

Minoxidil is used to treat recalcitrant hypertension. In one report of 1982 it was implicated in bilateral pleural and pericardial effusion formation in one patient (3). Pleural fluid was exudative and after exclusion of infection, malignancy and connective tissue disorder Minoxidil was discontinued and effusions disappeared. After rechallenge with the drug, only pericardial fluid recurred.

Amiodarone

A class III antiarrhythmic drug used commonly for the treatment of supraventricular and ventricular arrhythmias.

Table 1. The Naranjo adverse drug reaction probability scale; To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score

	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event occur after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total	

The Naranjo adverse drug reaction (ADR) probability scale. The Naranjo criteria classify the probability that an adverse event is related to drug therapy based on a list of weighted questions, which examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, dose - response relationships and previous patient experience with the medication. The ADR is assigned to a probability category from the total score as follows: definite if the overall score is 9 or greater, probable for a score of 5-8, possible for 1-4 and doubtful if the score is 0. The Naranjo criteria do not take into account drug-drug interactions. Drugs are evaluated individually for causality, and points deducted if another factor may have resulted in the adverse event, thereby weakening the causal association.

It has an extensive side-effect profile and every organ can be affected. Pleuro-pulmonary adverse reactions occur in approximately 5-10% of patients, and most often manifested as alveolar and interstitial infiltrates or pleural thickening. Rarely, pulmonary nodules or pleural effusions occur. Amiodarone toxicity is dose-dependent (>400mg daily) and appears 2 to 30 weeks after first administration. Pleural effusions have been reported to appear 2.5 months to almost 6 years after initiating the drug, but most patients develop pleural effusion after 6 months of therapy. Pleural effusion usually accompanies lung disease. There are however three case reports (4-6) on pleural effusion occuirng in the absence of clinically evident parenchymal involvement. Typically, the effusions are bilateral, asymmetric in size, but may be unilateral. Symptoms include progressive dyspnea, non productive cough, fever and weight loss. In most cases the fluid is a lymphocytic exudate. Foamy macrophages have been observed similar to those observed in BAL4. A patient with a neutrophil-predominent exudate without foamy macrophages, occurring 4 weeks after a dose increase has been also reported (6). The patient also complained of severe chest pain and the fluid had a tendency to loculate (6). Treatment consists in drug discontinuation and corticosteroid administration (although no randomized studies confirm this practice), depending on the patient's clinical condition. Improvement is usually expected to occur 1-3 months after stopping Amiodarone and commencing corticosteroids.

Beta-blockers

Mostly Practolol (not currently in use) and Oxyprenolol have been implicated in causing pleural effusion or pleural fibrosis. Oxyprenolol in particular provokes pleural fibrosis that progresses despite drug discontinuation and corticosteroid administration (7).

Calcium Channel Blockers

Diltiazem was reported to cause bilateral eosinophilic pleural effusion with peripheral eosinophilia. The effusion occurred 2 months after drug initiation and resolved after discontinuation. No rechallenge was attmpted (8).

Imidapril

In a recent study Imidapril use was linked with development of unilateral eosinophilic pleuritis (38% eosinophils) and peripheral eosinophilia in a patient, 8 years after initiating the drug. The patient initially developed low grade fever, dry cough and dyspnea, while peripheral eosinophilia was observed a year in advance. Pleural fluid was an exudate with low LDH levels and resolved 6 days after drug

discontinuation along with the peripheral eosinophilia. No rechallenge was attempted and the pleural effusion did not relapse (9).

Ramipril

It was implicated in the development of pleuropericardial effusion and cardiac tamponade (10). The patient was on a four-drug antihypertensive regimen for the last 10 years. All drugs were discontinued upon admission because the patient was hypotensive and corticosteroids were given for suspected myocarditis. After discharge the patient received again Ramipril only and symptoms recurred within a week. Pleural fluid was never aspirated and he was given corticosteroids anew (10).

Ergot Derivatives

They have been used for the treatment of migraine and cluster headaches (methysergide, ergotamine) or Parkinson's disease (bromocriptine, dihydroergotamine, nicergoline, pergolide, dopergine etc.). The characteristic lesions of the pleura develop after long term use and consist of pleural fibrosis with or without pleural effusion. Other organs and sites like the retroperitoneal space, the mediastinum, the pericardium and the cardiac valves may develop concomitant fibrosis. These lesions were first described in 1966 and have been confirmed in many reports ever since (11). The pathogenetic mechanism of fibrinogenesis is not clear and is postulated to be related to the serotoninergic activity of these drugs. It has been also postulated that pleural lesions may be combined with sub-clinical asbestos exposure (12,13). Respiratory symptoms develop 6 months to 30 years after initial exposure. Patients usually present with progressive dyspnea with or without dry cough, pleuritic chest pain, malaise and low grade fever. Radiologic findings include bilateral or unilateral pleural thickening with or without pleural effusion. Pleural fluid is exudative, usually lymphocytic and rarely eosinophilic. Hemothorax has been described with the use of methysergide (14). Laboratory findings include elevated ESR and CRP levls, normochromic anemia and weakly positive ANA and RF. Discontinuation of the drug is usually sufficient to induce progressive symptom improvement within months to years. Not uncommonly residual pleural thickening persists. Parenchymal pulmonary lesions usually improve rapidly. Corticosteroids are commonly used, without adequate proof supporting this practice.

Methysergide in particular causes pulmonary and pleural side-effects in about 1% of cases (15). Pleural fluid is exudative, paucicellular, clear or bloody. Pleural biopsies show mononuclear inflammation and fibroblast proliferation. Bromocriptine causes lesions to the lung and pleura in about 6% (15). Usual findings are pleural thickening and parenchymal lesions occurring 12 to 48 months after first administration. Two cases of eosinophilic pleural effusions have been described with Bromocriptine. Cabergoline was reported to cause bilateral pleural effusion and peripheral edema in a patient 3 years after first comencing the drug. The symptoms could not be attributed to any other cause and after drug withdrawal all symptoms and signs gradually disappeared. The association was deemed probable (16). Pergolide has been associated with rounded atelectasis and symptomatic diffuse restrictive pleural disease in a patient with no asbestos exposure (17).

Biological Agents

Biological agents are a relatively new drug class that keeps evolving as new agents are constantly discovered and new indications are assigned to existing agents. As biological agents are increasingly used, it might be anticipated that more and more of these agents will appear in the list of drugs inducing pleural disease (18).

Interleukin-2 (19)

It is used for the treatment of renal cancer and melanoma. Pulmonary side-effects occur in about 75% of patients, especially in those receiving bolus treatments instead of drip intravenous therapy. Pleural effusions occur in about 50% of patients and may be associated with pulmonary edema both attributed to increased capillary permeability. A minority of patients will require mechanical respiratory support. Pleural effusions resolve upon drug discontinuation and they are present in less than 20% of patients four weeks later.

Interleukin-11

It is used for severe chemotherapy-induced thrombocytopenia prevention. Fluid retention is the most frequent adverse effect and in one study of breast cancer patients 42% of them, developed pleural effusion (20).

Tyrosine Kinase Inhibitors Dasatinib and Imatinib

They are employed for the treatment of chronic myelogenous leukemia (CML) and acute lymphocytic leukemia with positive Philadelphia chromosome. A common adverse effect of Imatinib is fluid retention leading to pleural effusion formation, in approximately 1% of patients. Diuretic treatment is effective. An exudative pleural effusion occuirng two days after starting Imatinib that resolved after drug discontinuation and relapsed after readministration has been also reported (21). Dasatinib is a newer agent used to treat patients with CML refractory or intolerant to Imatinib. It is associated with the development of lung parenchymal disease and pleural effusions observed in 7-35% of patients with the risk being dose- and regiment-dependent (22). The frequency of Dasatinib-induced pleural effusion appears to be higher with twice daily dosing compared to once daily

dosing and in accelerated and blastic phase CML (23). The mechanism is not clear but an immune-mediated process is suspected due to the lymphocytic nature of the effusion and the association with a history of auto-immune disease and rash (22). Pleural effusions can develop at any time after commencing Dasatinib though usually appear between 5 to 32 weeks (23). They are bilateral in up to 79% of cases (24). Concurrent pericardial effusions are seen on CT scan or echocardiography in up to 29% of cases (24). Symptoms include cough, dyspnea and chest pain. Pleural fluid is usually a lymphocytic exudate and lymphocytic infiltration of the pleura has been observed (21). Chylothorax without evidence of chyle leak and transudative effusions have been also reported (21). Dasatinib-induced pleural effusion are associated with the presence and the number of large granular lymphocytes, another side-effect of the drug (24,25).

Pleural effusions usually resolve within four weeks after drug discontinuation. Symptomatic patients with large pleural effusions may also require a therapeutic thoracentesis and a short course of prednisone (40 mg of prednisone in for four days) (22). Corticosteroids may hasten symptomatic and radiologic resolution. After resolution of the pleural effusion the drug can be re-introduced, ideally in a lower dose, in a single dose regiment and definitive discontinuation of the drug can be considered if a large or a symptomatic effusion relapses (22).

Bortezomib

It is used to treat patients multiple myeloma and implicated in bilateral pleural effusion formation in the context of diffuse alveolar damage and ARDS (26).

Immunoglobulin

A patient with idiopathic thrombocytopenic purpura presented with bilateral lymphocytic exudates on the 7th or 8th course of immunoglobulin treatment. The effusion could be not attributed to any other cause (27). Because the effusions did not reappear after administration of a different preparation, a reaction to a component of the first preparation was suspected.

G-CSF

Its use has been associated with pleural fluid formation that developed in patients with different diseases and have variable characteristics. In a chemotherapy-induced neutropenic patient a unilateral pleural effusion occurred ten days after commencing the agent and fluid analysis showed immature myeloid cells. The effusion resolved gradually after drug discontinuation (28). In another case of a patient with rheumatoid arthritis, renal insufficiency and methotrexate-induced pancytopenia, bilateral pleural effusions developed, nine days after starting G-CSF treatment. The effusions resolved 20 days after drug discontinuation and corticosteroid treatment (29). The most reliable report regards a case of life threatening capillary leak syndrome after G-CSF administration in a healthy leukocyte donor. The patient developed acutely hypotension, hypoxemia, generalized edema, ascites, pericardial and bilateral pleural effusion. The drug was discontinued, intravenous fluids and corticosteroid pulses were administered and the patient fully recovered (30).

Chemotherapy Agents

Bleomycin (31)

It used to treat different malignancies and causes a multitude of adverse effects implicating the lung and the pleura in 6-10% of patients. Toxicity is dose-dependent and more common in older patients or patients receiving oxygen, radiation therapy or other chemotherapy agents. Pleural effusions develop in a small percentage of patients with pneumonitis.

Procararbazine (32)

Two cases of hypersensitivity reactions have been described. Both patients presented with fever, cough, dyspnea, peripheral eosinophilia, pulmonary infiltrates and bilateral or unilateral effusions. Signs and symptoms resolved after drug discontinuation, and recurred after rechallenge. The drug was discontinued permanently, corticosteroids were administered and symptoms resolved completely.

Methotrexate

When administered in high doses it has been associated with development of pleuritic chest pain appearing 2 to 5 days after treatment initiation in 4% of patients from which 30% eventually developed pleural effusion (33). In another study, 8% of patients treated with weekly regimen of large methotrexate doses developed pleuritic chest pain (usually on the right side) with ipsilateral pleural thickening (34). Pain subsided in 3-5 days after drug discontinuation and relapsed after readministration. Pleural thickening did not improve.

Cyclophosphamide

Pleural thickening has been reported to accompany late onset pneumonitis that manifests years after first exposure. Patients complain of insidious onset of dyspnea and cough (35). Reticular or reticulonodular infiltrates with pleural thickening is the characteristic radiological pattern. The disease usually progresses without response to corticosteroids. A case of bilateral transudative pleural effusion in a 37 year old patient 2 days after receiving high doses of Cyclophosphamide before bone marrow transplantation has been also reported (36).

Mitomycin
It may rarely cause severe bilateral interstitial pneumonia with or without bilateral pleural effusion (37).

Decitabine (38)
It is used for the treatment of patients with myelodysplastic syndrome (MDS). There is a report of a 60 year old patient with MDS who developed fever, pleural and pericardial effusion. The patient initially presented with fever and neutropenia followed by (2 weeks later) the appearance of left sided pleural and pericardial effusion. The fluid was a lymphocytic exudate. The patient was discharged and 14 weeks later both effusions disappeared.

Erlotinib
There is a report of a patient with malignant pleural effusion (adenocarcinoma) that developed fever, cough and increasing breathlessness 12 days after starting the EGFR tyrosine kinase inhibitor Erlotinib. The pre-existing unilateral pleural effusion had increased significantly in size although the tumor had reportedly responded to Erlotinib. The correlation between the effusion and the drug is very weak and rechallenge did not result in pleural fluid re-accumulation (although the patient had been subjected to talc pleurodesis) (39).

Anticoagulants
In a small percentage of patients, use of anticoagulation agents can cause spontaneous hemothorax. This is observed mostly in patients receiving anticoagulation therapy for pulmonary embolism but has been reported also after angioplasty or pneumonia and is not correlated with "pathologically" elevated coagulation times (18,40). A case of eosinophilic pleural effusion has been reported 9 months after initiation of warfarin treatment (41). It resolved after drug discontinuation and relapsed after re-challenge. A case of Ticlopidin-related hemothorax 28 days after chest trauma with rib fractures has been reported (42).

Ovarian Hyperstimulation Syndrome (43,44)
The use of follicular stimulating drugs has been associated with ovarian hyperstimulation syndrome with increased morbidity and mortality. The syndrome is characterized by exavasation of protein-rich fluid in the peritoneal, pleural and rarely in the pericardial cavities. The cliinical intensity of the syndrome depends on the response of the ovarian follicle to the follicle stimulating factor and in its most severe form is characterized by hypovolemic shock, hemoconcentration, acute renal and respiratory failure and coagulation disorders. Respiratory physicians unlike gynecologists are not for the most part familiar with this syndrome. There are many reports in the literature where the syndrome even in its severe form manifests with unilateral pleural effusion without concomitant ascites. The fluid is usually exudative but in some cases can be transudative in nature. Symptoms include chest pain, dyspnea and cough and occur 3-7 days after initial exposure to follicular stimulating agents. When the syndrome occurs later is usually more severe and if pregnancy does not ensue the syndrome resolves after a week approximately. If pregnancy ensues it can last up to 20 days. In milder forms treatment consists in colloid solution administration and pleural cavity evacuation is reserved for more severe cases.

Sclerotherapy Agents (15)
Endoscopic instillation of sclerotherapy agents for the treatment of esophageal varices has been associated with pleural effusion formation. Most probably it is secondary to the inflammation from the esophagus that expands to the mediastinal pleura. The effusion is more common on the right side although it depends on the site of instillation. It occurs within 24 hours and resolves automatically within a week. Rarely can it be complicated by empyema.

Drug Induced Eosinophilic Pleural Effusion
When pleural fluid eosinophils reach or exceed 10% of total nucleated cells, this is called an eosinophilic pleural effusion. It is not indicative of any specific disease and cannot be used to establish a diagnosis, since a number of drugs are known to cause both eosinophilic and non-eosinophilic pleural effusions. For historic reasons eosinophilic pleural effusions are reported separately and the following six drugs are usually mentioned as typical cause eosinophilic pleural effusion.

Valproic Acid
There is one report dated in 1995 of a patient treated with Valproic acid for 9 months for epilepsy that developed eosinophilic pleural effusion on the left hemithorax with concomitant peripheral eosinophilia. Pleural fluid and blood eosinophils were 62% and 26%, respectively. The effusion resolved completely 6 months after drug discontinuation. The fact that that patient had completed treatment for left lower lobe pneumonia just a week before the pleural effusion was discovered, casts serious doubt on the validity of the proposed diagnosis (45). There are however at least 5 other more recent cases showing that valproic acid is a probable cause of eosinophilic pleural effusion (46). In general peripheral eosinophilia is often but not always found. The fluid is exudative, with an eosinophil percentage of at least 40% and often a pH >7,50 in most of the cases reporting a pH measurement. The effusions may be unilateral or bilateral and in all cases resolve within 6 months after drug discontinuation. In account of the local and peripheral eosinophilia a hypersensitivity reaction is most likely the underlying pathogenetic mechanism (46).

New case reports continue to appear in the literature (47,48), the most interesting one describing a case of bilateral transudative pleural effusion. The patient had been receiving the drug for a year and presented with fever, dry cough, dyspnea and unilateral pleural effusion (on chest radiograph). The patient had a similar episode 8 months before and the pleural effusion was a neutrophilic transudate. After therapeutic thoracocentesis, pleural fluid reaccumulated and bilateral pleural effusions were observed on a thoracic CT. Because of the unremarkable findings in the extensive work-up that followed, and considering the patients' normal echocardiography a drug reaction was supsected and the drug was replaced. The patient improved within days and on unintentional rechallenge (the patient changed back to Sodium Valproate after an epileptic episode without consulting his physician) the patient relapsed within a month (49).

Nitrofurantoin

It is used for the treatment of urinary tract infections. Since 1962 when the first case (50) was described more than 2000 cases of pulmonary and pleural adverse effects have been associated with the use of Nitrofurantoin. These adverse effects are classified as acute, subacute and chronic. Acute reactions are observed in 5-25% of patients. They are hypersensitivity reactions occuring within days or hours and are not dose-dependent. Patients complain of cough, dyspnea and fever. Alveolar and interstitial infiltrates are also observed. Pleural effusions, often bilateral, appear in one third of these patients with lung involvement but they do not appear as an isolated disorder. Peripheral eosinophilia is impressive (as high as 83%) and is evident much more often than pleural fluid eosinophilia. Treatment consists in drug discontinuation and corticosteroid treatment in more severe cases. Chronic reactions to Nitrofurantoin are more subtle and consist in pneumonitis and fibrosis. Pleural involvement is much rarer and consists in pleural thickening and pleural fibrosis. Pleural involvement is time and dose dependent. Despite drug discontinuation, lesions do not resolve and may even progress.

Dantrolene (15)

It has a similar chemical structure to that of Nitrofurantoin and is used as a muscle relaxant. Eosinophilic pleural effusions have been reported in 6 patients receiving the drug for 2 months up to 12 years. Patients typically present with pleuritic chest pain and fever. Pleural effusion was typically unilateral, exudative, with normal glucose levels and very high eosinophil count (33%-66%). Usually there is also peripheral eosinophilia (7%-18%) and pericarditis. Lung lesions were not reported in any of the patients. Drug discontinuation leads to rapid symptom improvement and slower pleural fluid resolution. Corticosteroid treatment may hasten pleural fluid absorption.

Isotretinoin (18)

It is used to treat cystic acne. There have been reports of unilateral eosinophilic pleural effusion 1-7 months after initiating treatment with isotretinoin. Symptoms can be subtle with insidious onset of dyspnea or can appear acutely with fever and cough. Neither peripheral eosinophilia nor pulmonary infiltrates were observed. Effusions disappeared 1-3 months after drug discontinuation.

Propylthiouracil

It is used for the treatment of Graves disease. There has been a report of a patient who being in treatment with the drug for 3 weeks developed pleuritic chest pain and eosinophilic pleural effusion without lung infiltrates or peripheral eosinophilia. At the initial thoracocentesis eosinophils were 16% of total nucleated cells and 2 weeks later while still receiving the drug, eosinophils rised to 45%. The pleural effusion resolved completely three months after drug discontinuation (51). A second much more recent report corroborates these findings. In this case, pleural effusion developed after 11 years of Propylthiouracil treatment and did not resolve by drug discontinuation alone. Corticosteroids led to rapid and complete resolution of the effusion. Re-challenge was attempted and the pleural effusion recurred (52).

Glyclazide (53)

A 52 year-old patient with a moderate sized pleural effusion and concomitant pulmonary infiltrates appeared two weeks after exposure to Glyclazide has been described. Pleural fluid and blood eosinophils were 80% and 20%, respectively. Full radiologic and clinical recovery was reported a month after drug discontinuation.

Miscellaneous Drugs

Acyclovir

There is a report on a patient who three days after starting treatment with Acyclovir developed fever and bilateral pulmonary infiltrates (54). The next day the patient also developed left sided pleural effusion and hemoptysis. After excluding pulmonary embolism and infection the drug was discontinued and the fever resolved immediately; ten latter days so did the pulmonary infiltrates and the pleural effusion.

Clozapine (18)

A commonly used neuroleptic drug that has been associated with pleural effusion in at least five cases. The effusions developed 7 days to 2 months after drug exposure and were more commonly bilateral with or without pericardial effusion. Symptoms were non specific and

included pleuritic chest pain, fever, rash and peripheral eosinophilia while some patients were completely asymptomatic. The effusion was sampled in only one patient and the fluid was an exudate with neutrophil predominance. Another patient with bilateral pleural effusions presented with symptoms of systemic disease with concomitant hepatitis and glomerulonephritis. Symptoms and radiologic findings resolve within days of drug discontinuation and re-challenge in two patients led to immediate symptom relapse.

Itraconazole (55)

A case of exudative pleural effusion two months after starting Itraconazole treatment for invasive aspergillosis has been reported. A week later the patient also developed pericardial effusion that required drainage. Rechallenge with the drug lead to the development of pulmonary infiltrates and heart failure that could not be attributed to any other cause.

L-Tryptophan

It is used in many over the counter preparations as a sleep-promoting drug. It causes eosinophilia-myalgia syndrome, a systemic disorder that may include bilateral pulmonary infiltrates and pleural effusions. Drug withdrawal and corticosteroids lead to swift full recovery (56).

Mesalamine

It is used to treat inflammatory bowel disease and has been associated with pulmonary infiltrates with or without pleural effusion. Eosinophilic pleural effusion with pulmonary infiltrates and peripheral eosinophilia that resolved after drug withdrawal and corticosteroid administration has also been reported. Mesalamine has also been associated with pleuropericarditis without pulmonary infiltrates 2 weeks after first exposure in a patient with ulcerative colitis. Symptoms included fever, chest pain and malaise. Although the patient improved soon after drug withdrawal and aspirin addition, symptoms reappeared after the drug re-administration. Mesalamine was discontinued permanently and corticosteroids were used (57). Mesalamine is also known to cause drug induced lupus (58).

Simvastatin

A patient developed cough, malaise and progressive dyspnea six months after first receiving the drug. The chest x-ray showed bilateral pulmonary infiltrates and right-sided pleural effusion. The patient also had elevated liver enzymes and IgE. The BAL had 34% eosinophils and pleural fluid had a brownish color. Pleural fluid features were not reported. Drug withdrawal and corticosteroids led to full recovery (59).

Pravastin

We have reported on a patient with a symptomatic bilateral pleural effusion receiving 40mg of Pravastin for 12 months. The fluid was a lymphocytic exudate. Despite extensive diagnostic work-up, including a fine needle pleural biopsy, a definite diagnosis could not be established and Pravastin was discontinued. Complete resolution of the effusion was reported within 2 months and no signs of relapse were reported during follow-up (60).

Troglitazone

It is used to treat diabetes mellitus. A patient developed productive cough, dyspnea and nocturnal perspiration a week after the first dose. Chest x-ray revealed small bilateral pleural effusions with interstitial basal infiltrates. Symptoms and radiological signs resolved a few days after drug discontinuation. A causal relationship was assumed based only on temporal association (61).

Pioglitazone

It is also used to treat diabetes mellitus. A patient with normal cardiac function who was receiving the drug for five months developed massive bilateral pleural effusion and anasarca. The effusion was transudative and although the patient was receiving other medication, the effusion did not resolve (although it did improve) with diuretics and disappeared only after Pioglitazone was discontinued, indicating a probable adverse drug reaction (62).

Insulin

There are a few reports that insulin therapy in poorly controlled type 1 diabetic patients can cause fluid retention that may even progress to cardiac failure. A recent article reported on a patient with type 2 diabetes who developed pleural and pericardial effusion along with peripheral edema a week after starting regular and NPH insulin. The patient was treated with diuretics (63).

Tinazidine

It is used as a muscle relaxant. There is a case report of eosinophilic pleural effusion development in a 42-year-old patient six weeks after starting treatment with Tinazidine. Despite the significant amount of pleural effusion, the patient was asymptomatic, probably due to systemic opioid use. There were no other remarkable symptoms or laboratory findings. The effusion disappeared within 4 weeks after drug discontinuation (64).

Fluoxetine

It is used for the treatment of depression and in a case report is associated in eosinophilic pleural effusion formation with peripheral eosinophilia and pleuritic chest pain. The patient was receiving the drug for eight weeks and it took as much time to full recovery after drug discontinuation (65).

Sirolimus

Sirolimus has been described to cause pleural effusions, ascites and peripheral edema in liver transplant patients. A lung transplant patient, two months after initiating ttreatment with Sirolimus developed progressive airway obstruction followed by bilateral pleural effusions in combination with proteinuria and peripheral edema, despite being in high doses of methylprednisolone. After Sirolimus discontinuation, pulmonary function tests improved rapidly but the effusion persisted for 6 months (66).

Drug Induced Lupus (DIL) Pleuritis

Since first description of the syndrome in 1945, the list of drugs known to cause drug induced Lupus (DIL) keeps growing. The main differences between drug induced and idiopathic Lupus (SLE) are: a) DIL is reversible with drug discontinuation; b) there is no gender preference; c) DIL is generally milder and the predominant symptoms are arthralgias, myalgias, rash and serositis while unlike idiopathic SLE, kidney and CNS involvement is rare.

Drug induced Lupus pleuritis is by far the most common cause of drug induced pleural effusion with thousands new cases reported every year. Pleural effusions are typically bilateral and are the most common radiologic finding of the disease. Pericarditis and pulmonary infiltrates may coexist. Patients are usually symptomatic and pleural fluid is exudative with varying total number of nucleated cells and glucose levels similar to those of serum. Pleural fluid ANA levels are typically manifold to those of the serum while LE cells are rarely found but they are pathognomonic. ESR and serum ANA titers are elevated. Histone antibodies which are found in 50-80% of cases are suggestive, but not specific of DIL. High anti-dsDNA antibody titers and low complement levels are characteristic of idiopathic Lupus, but they are very rare in DIL (<1%), with the exception of anti-TNF agent-induced Lupus. Care should be taken, to avoid administration of drugs known to cause Lupus to people with known SLE because symptoms may be aggravated.

Drugs most frequently related to DIL induction are:

Procainamide (18)

It is the drug most commonly associated with DIL. Over 90% of patients receiving Procainamide will have positive ANA within the first year of treatment. Approximately 1/3 of these patients will develop DIL within a period ranging from 1 month to 12 years after first exposure and >50% of them will have pleural effusion.

Hydralazine (67)

Half of the patients receiving Hydralazine, an antiarrhythmic agent develop ANA at some point. However, only 2-20% will present the syndrome, most often women with a slow acetylator phenotype and after a cumulative dose of 100gr. Typical symptoms include arthralgias and fever. Pleural effusion is present only in 30% of these patients.

Isoniazid (15,18)

Isoniazid induces positive ANA in a quarter of the patients receiving it, though very rarely causes DIL. The “paradoxical response” in which pleural effusion appears or increases in size in patients receiving anti-tuberculous treatment for 3-12 weeks, complicates the diagnosis of drug DIL-pleuritis. There have been reports of pleural effusions that were thought to be paradoxical responses that were compatible with DIL (lymphocytic exudate with normal glucose levels, high ANA titers, low ADA and complement). In patients receiving Isoniazide bilateral pleural effusions with pericarditis, rash and joint pain should direct the clinician towards DIL. Normal serum ANA titers almost completely exclude DIL.

Quinidine (15)

Thirty cases of patients with Quinidine induced Lupus have been reported. Apart from serositis, symptoms included arthritis and rash.

D-penicillamine

This chelating and immunoregulatory agent can cause pleuritis in the context of Lupus like syndrome, but a unilateral exudative pleural effusion without serological findings compatible with DIL has also been reported. The effusion appeared 12 years after the first dose of the drug and relapsed despite repeated thoracocentesis and pleurodesis attempts. The patient had to undergo decortication to control symptoms and the pleural biopsy established chronic inflammation. The drug was never discontinued (68).

Anti-TNF Agents Infliximab and Etanercept

They are widely used for the treatment of rheumatoid arthritis, psoriasic arthritis and Crohn’s disease. They have been implicated in DIL and associated pleuritis. Clinically evident DIL was reported in 0.22% after a mean time of about nine (range: 3-16) months since commencing the drug. For Etanercept, FDA had recorded 22 cases between 1998-2002 with a percentage of clinically evident lupus of 0.18%, similar to that of infliximab and a mean time of occurrence of 4 months (2-5) (69-71). In the few reports of anti-TNF agents induced lupus pleuritis, pleural effusions were exudative, with normal pH, unilateral or bilateral, with concomitant pericardial effusion. All patients had fever and compatible with DIL clinical symptoms and serologic findings. Pleural biopsies showed remarkable pleural thickening or pleural and adjacent lung inflammation. All patients improved within six weeks after drug discontinuation and short term corticosteroid treatment. Clarification of the

pathogenetic mechanisms involved in this adverse effect, will surely give important insights to the pathogenesis of connective tissue disorders since they probably represent cases of skewed autoimmunity rather than common drug reactions (72-74).

Conclusion

A wide variety of drugs may cause pleural disorders. Pleural disease as a drug adverse effect is generally underappreciated, especially by non-respiratory physicians. The possibility however should not be overlooked in a patient with a pleural effusion that can not be attributed to a more common etiology after the initial work-up. As new drugs are being constantly introduced, association of a new drug with a pleural manifestation will be a challenging task. Experience with the drug will be limited, mechanisms of action not fully studied and adverse effects not overtly recognized. Moreover, drug discontinuation may be more difficult since alternative agents may be limited or even non-existent. Therefore a meticulous history of drug intake including temporal association between drug exposure and symptoms should alert the clinician on the possibility of drug induced pleural disease. This way patient discomfort will be avoided, unwarranted discontinuation of potentially irreplaceable drugs will be averted and the need for unnecessary and possibly harmful invasive procedures will be obviated.

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