

Case Report

Minimal Change Disease Associated with Malignant Epithelioid

Mesothelioma: A Case Report

Christina Danai Skondra^{1*}, Christalleni Christodoulidou¹, Theodoros Tegos², Christina Vourlakou³,
Aggeliki Paikopoulou¹, Konstantinos Folinis², Styliani Plavoukou¹, Nikolina Stavrinou³, Konstantinos
Christofidis³, Chara Gakiopoulou⁴, Nektarios Alevizopoulos² & Michael Vaslamatzis²

¹ Department of Nephrology, Evangelismos General Hospital, Athens, Greece

² Department of Oncology, Evangelismos General Hospital, Athens, Greece

³ Department of Pathology, Evangelismos General Hospital, Athens, Greece

⁴ Department of Pathology, Laiko Hospital, National and Kapodistrian University of Athens, Greece

* Corresponding author, Dr. med Christina Danai Skondra, E-mail: christinadsc@hotmail.com

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Abstract

We report the case of a 64 year old male patient with a recent diagnose of pulmonary nodules with pleural thickening who was admitted to the nephrology department of our hospital for further evaluation of nephrotic syndrome (NS). Malignant epithelioid mesothelioma (MEM) was diagnosed after pleural biopsy while the renal biopsy showed minimal change disease (MCD) with acute tubular necrosis and interstitial lymphoplasmacytic infiltrate.

MCD is the most common cause of nephrotic syndrome in children while it accounts for a smaller proportion of NS in adults. The underlying cause of MCD is unclear (Cameron, 1987). Evidence so far suggests that T-cell dysfunction results in the production of a circulating factor directly affecting the glomerular capillary wall with consequent foot process fusion. MCD as paraneoplastic syndrome is common in hematological disorder while the incidence in lung pulmonary malignancies is rare. Early recognition leads to an early diagnosis of malignancy improving the outcome and diminishing the associated co-morbidities.

Keywords

malignant epithelial mesothelioma, nephrotic syndrome, paraneoplastic syndrome

1. Case Report

A 64-year old male patient was referred to our hospital from the Cardiology department of a peripheral hospital for further evaluation of acute kidney injury with oliguria and nephrotic range proteinuria. The patient was initially admitted to the other hospital because of acute onset edema, dyspnea and weight gain of 8 kg within the last two weeks. According to his medical history, the patient had been well, until his first hospitalization two years before the diagnosis of MCD (9/2017) due to a community acquired pneumonia with exudative right-sided pleural effusion. A year ago (8/2018) he was hospitalized again because of pulmonary embolism without detectable trigger. The coagulation test showed a positive Lupus anticoagulant (La) while the anticardiolipin antibodies and the anti beta2 glucoprotein antibodies were normal. An oral anticoagulation therapy with Rivaroxaban was initiated.

A computer tomography had been performed two months before the hospitalization (9/2019) in our division because of persistent cough and weight loss, which showed pleural thickening with effusion and osteolytic lesions of the right 5th and the 7th ribs, bilateral multiple solitary pulmonary nodules and mediastinal lymph nodes. All those findings raised the clinical suspicion for a mesothelioma. The patient was further evaluated with bronchoscopy and endobronchial ultrasound (EBUS) guided biopsy of the mediastinal lymph nodes, which result was still not available at the time of the admission.

The clinical evaluation on November 2019 revealed a man in good condition with pitting edema in both legs and blood pressure of 125/70 mmHg. The laboratory data showed severe hypoalbuminemia (2.1 mg/dl) and nephrotic range proteinuria (10 gr/24 h) with all findings suggesting nephrotic syndrome. The creatinine was 3.7 mg/dl with a normal baseline creatinine of 0.8 mg/dl three months ago. The autoimmune diagnostic was normal except of positive ANA's title (1:640). The serum protein electrophoresis was normal too.

The renal ultrasound showed no signs of dilation or obstruction of the pelvicalyceal system and a diagnosis of renal vein thrombosis was ruled out by a triplex ultrasound. Echocardiography showed normal systolic and diastolic function without signs of valvular disease. At that time we received the pathology report that described morphological and immunohistochemical features confirming the diagnosis of malignant epithelioid mesothelioma [Calretinin (+), D2-40(+), CK 7 (+), CK 5/6 (+), TTF 1 (-), p40 (-), Napsin A (-), BerEP4 (-) CK 20 (-)] (Images 1-4)

We performed a renal biopsy which contained 50 glomeruli without signs of glomerular disease but with acute tubular necrosis and interstitial lymphoplasmacytic infiltrate in the light microscopy examination, negative staining on immunofluorescence and extensive foot process fusion without evidence of electron dense deposits on the electron microscope. (Images 5-8)

A diagnosis of nephrotic syndrome secondary to MCD was confirmed, and we started with oral corticosteroids (1 mg/kg), PPIs and subcutaneous low molecular weight heparin. We contacted at the same time the oncology department of our hospital and chemotherapy with carboplatin and gemcitabine was initiated.

2. Outcome and Follow up

Four weeks after the initiation of corticosteroids the proteinuria significantly decreased to 1.6 gr/24h and creatinine level returned to baseline (0.9 mg/dl). Because of the achievement of partial remission we started a tapering of the steroid dose. On Jan 2020 he reached a complete remission of his proteinuria and the corticosteroids were completely stopped.

On March 2020 and after 6 doses of Carboplatin and Gemcitabine, the follow up PET CT revealed a new osteolytic lesion in the 6th pleura right with a progression of the solitary pulmonary nodules in the low right lobe and a hepatic metastasis. A radiotherapy including the 5th, 6th, 7th and the 8th ribs was contacted in a total dose of 50 Gy and a 2nd line chemotherapy with Pemetrexed and Navelbine was started. On 6/2020 we were called for consultation because of a relapse of the proteinuria with edema and hypoalbuminemia along with acute kidney injury. Because of the steroid responsiveness at the first NS an induction therapy with corticosteroids was initiated again with a good response. Unfortunately, the patient died 3 months later due to sepsis and multiorgan failure.

3. Discussion

Malignant mesothelioma is an asbestos-associated rare and insidious neoplasm with an annual incidence of 1.1-1.25/100.000 and approximately 2000 estimated cases in Europe and 3000 in the United States (Robinson, 2012; Price, 1997). The incidence of mesothelioma in the United States and in many other countries peaked around the year 2000 and is now declining, secondary to control of exposure to asbestos.

Eighty percent of cases are of pleural origin. The predominant cause of MEM is inhalational exposure to asbestos with approximately 70% of cases of the disease being associated with documented asbestos exposure. Occupational asbestos exposure is the most important risk factor for subsequent development of the disease, with a latency period of almost 20 years after exposure.

Most cases of mesothelioma not related to asbestos are considered as idiopathic. However, in certain geographic areas, mineral fibers other than asbestos (e.g., erionite, fluoroedenite, Carbon nanotubes) have been linked to mesothelioma. Therapeutic radiation for other malignancies, viral oncogenes (SV40) and genetic factors are another risk factor (Sternan, 2005).

Environmental, non-occupational exposure to asbestos is an interesting topic of the epidemiology of mesothelioma. In certain rural areas in Greece, Turkey, and Bulgaria soil contains high levels of tremolite asbestos fibers and many cases of mesothelioma in these regions appear to be related with this type of long-term non-occupational asbestos exposure. Especially in Cappadocia, Turkey, the inhalation of other fibrous silicates, such as erionite, has been related to high incidence of pleural mesothelioma of this region (Carbone, 2007; Bayram, 2013). A role for non-occupational exposure to asbestos was also supported by a study from California in which an increased incidence of mesothelioma was associated with proximity to naturally-occurring asbestos deposits (Pan, 2005).

Fluoroedenite is a naturally-occurring mineral that forms amphibole asbestos fibers. Unpaved roads in Biancavilla, Sicily, Italy, are a source of airborne fibers and it seems that there is a strong epidemiological link with the development of mesothelioma, in the absence of occupational exposure (Bruno, 2014).

Our patient had no exposure to any of these risk factors, so it should be considered that he had an idiopathic malignant pleural mesothelioma. MEM arises from mesothelial surfaces of the pleural or/and peritoneal cavity, tunica vaginalis, or pericardium. More patients have advanced disease at presentation, so the prognosis of MEM is poor with a 6-month, 1 year and 5 year survival rate is 55, 33 and 5% respectively (Teta, 2008).

The most common symptoms of MEM are nonspecific such as chest pain, dyspnea, cough, hoarseness, night sweats or dysphagia, which occur in the setting of extensive intrathoracic disease, while systemic symptoms such as fever, weight loss and fatigue may also be present in patients with advanced disease. Symptoms may be present for months or longer, prior to diagnosis. Distant metastatic spread is less common but rarely can involve the bone, liver, or central nervous system (CNS). In very rare instances, patients with MEM present with acute symptoms of local invasion of vital structures. For example, brachial plexus involvement or compression of the spinal cord may lead to focal neurologic deficits. Growth through the diaphragm may lead to bowel obstruction resulting in abdominal pain, distension, and vomiting. Impingement on the superior vena cava may cause symptoms of head fullness or facial swelling. Cardiac involvement may lead to arrhythmias or heart failure (Milano, 2010; Bech, 2008; Tanriverdi, 2013).

The interesting about our case is that our patient presented with signs and symptoms of paraneoplastic nephrotic syndrome (peripheral edema, dyspnea, weight gain, proteinuria), while the symptoms from mesothelioma (chest pain, cough, hoarseness, night sweats, or dysphagia) were mild. The dyspnea of the patient was attributed to the retention of fluids. A number of paraneoplastic syndromes have been described rarely, in the setting of advanced stage of MEM, including fever, thrombocytosis, malignancy-related thrombosis, hypoglycemia and rarely, Coombs-positive hemolytic anemia (Richard, 2008).

Renal “damages”, such as vasculitis, neurologic disorders and thrombocytosis in relation to advanced MPM have already been rarely described in the international literature (Milano, 2010; Tanriverdi, 2013). The best known association between malignancy and MCD is that seen in Hodgkin’s lymphoma. Possible mechanisms to explain the association include the elaboration of vascular permeability factor, cytokines, and chemokines by tumor cells (Zucca, 2010). The first case of paraneoplastic nephrotic syndrome in association with malignant mesothelioma of the pleura, was published in 1986, in a 68-year-old man. Renal biopsy revealed minimal-change glomerular disease. The proteinuria did not respond to treatment with prednisone and cyclophosphamide but improved during treatment with doxorubicin hydrochloride and dacarbazine, without noticeable improvement in the tumor (Schroeter, 1986).

Conventional chemotherapy may induce nephrotoxicity with many ways including nephrotic syndrome. These drugs can promote kidney injury through a variety of mechanisms that may affect the glomeruli, tubular segments, interstitium and/or renal microvasculature (Rosner, 2017).

With the introduction of immune check point inhibitors (ICPI's) into the treatment of MPM, cases of nephrotic syndrome with MCD were observed as a side effect of this treatment (Bickel, 2016).

Patients with MEM and nephrotic syndrome without any of the above causes are considered to have MEM and paraneoplastic nephrotic syndrome. It should be noted that renal biopsy can give the diagnosis of the underlying histological disorder of nephrotic syndrome but not the cause of it. Our patient had not been previously treated with chemotherapy or cytotoxic T lymphocyte antigen-4 (CTLA-4) or programmed cell death receptor 1 (PD-1) and had no symptoms and signs or positive laboratory examinations of arterial thrombosis or mesenteric infarction or no coexistence of serositis except of a small pleural effusion on the right hemithorax. The patient had positive ANAs title (1:640) with no extrarenal manifestations as arthritis, rash, alopecia or ulcers and with negative autoimmune diagnostic examinations (anti dsDNA, RF, ENAs, serum and urine protein electrophoresis, C3, C4, b2GPIgM, IgG and ACL IgM and IgG) for SLE. Moreover, the patient did not take any DNA methylation inhibitors, well known that induce autoreactivity in vitro, and cause a lupus-like disease in vivo or other drugs that may influence the risk of developing disease, triggering an autoimmune response, such as procainamide, hydralazine or minocycline. The pleural effusion was attributed to the basic malignant disease since in the fluid examination there were only found mesothelial cells, while antinuclear antibody testing in pleural fluid was negative. Malignancy itself, triggers inflammation and may result in autoantibody production. The International literature describes only three cases of mesothelioma presenting with SLE seropositivity (Rakhra, 2019; Javierre, 2011). Thus, the patient was considered as having MEM with paraneoplastic nephrotic syndrome and underwent renal biopsy. The results of the renal biopsy with the specimen consisting by 50 glomeruli, revealed no signs of glomerular disease but acute tubular necrosis in the light optical microscope, negative staining on immunofluorescence and extensive foot process fusion without evidence of electron dense deposits on the electron microscope (images 4-7). The biopsy specimen did not show massive deposits of AA-type amyloid in the glomeruli, small arteries and medulla. Based on these findings, the diagnosis of nephrotic syndrome secondary to MCD was confirmed and we started with oral corticosteroids (1 mg/kg), PPIs and subcutaneous low molecular weight heparin.

MCD may occur in association with Hodgkin lymphoma and, less commonly, other lymphoproliferative disorders and has rarely been associated with solitary tumors. One putative mechanism is the secretion of a glomerular-toxic lymphokine by abnormal T-cells. Lymphoma-associated MCD is frequently resistant to treatment with glucocorticoids and cyclosporine, therefore, a poor response to the treatment of MCD with these agents should prompt an investigation for an underlying malignancy. In some but not all patients with lymphoma-associated MCD the course of MCD correlates with that of the lymphoma.

Glomerular disease in the setting of malignancy has been recognized for several decades. Most commonly, the glomerular pathology is membranous nephropathy (Da'as, 2001; Farmer, 2001). Renal lesions in the context of MPM are extremely unusual (Venzano, 1990; Tanaka, 1994; Galesic, 2000; Farmer, 2001; Bacchetta, 2009; Suzuki, 2014; Li, 2010; Dogan, 2012; Tsukamoto, 2015; Yildiz, 2016; Shibata, 2020; Xinyu, 2016; Fawole, 2012) with only 12 cases having been reported in the English-language literature (Table 1). Six of the reported cases presented MCD, three with membranous nephropathy, one with proliferative segmental GN and one AA amyloidosis. One patient refused the kidney biopsy. A case of IgA nephropathy is also documented in the literature but the patient did not present with nephrotic syndrome (Fawole, 2012).

The case we present is the only one among 156 patients with MPM consecutively admitted in the Department of Medical Oncology of Evaggelismos General Hospital, Athens Greece, among 31/3/1986 - 30/9/2020. MCD has been associated with hematological malignancies as Hodgkin lymphoma, although the underlying molecular link remains poorly understood and is probably associated with T-cell dysfunction (Cameron, 1987; Audard, 2006).

Podocyte injury is supposed to be mediated by cytokines like VEGF and an overwhelming immunologic response produced by malignant mesothelioma cells (Audard, 2006; Fitzpatrick, 1995) which are also responsible for the aggressive tumor growth. In our case the acute renal failure was most likely related to acute tubular necrosis in the setting of MCD. The mainstay of initial therapy of MCD is prednisone or prednisolone, with a large percentage of adults, particularly younger patients, achieving complete remission in a short time (maximum few months). We administered prednisolone in dose of 1mg/Kg/day but the response was partial and for a short duration as was the response of the main disease resulting in the patient's death 10 months after the onset of disease.

4. Conclusion

In summary, we present a rare case of MCD with acute kidney injury in a patient with malignant pleural epithelial mesothelioma. Treatment of the malignancy may accelerate the remission but the development of NS in the setting of mesothelioma is associated with poor prognosis. Further evaluation with kidney biopsy should be considered for patients with asbestos-related diseases with signs of glomerular disease and conversely it is important to increase awareness and recognize clinical contexts in malignancies in order to initiate a timely treatment.

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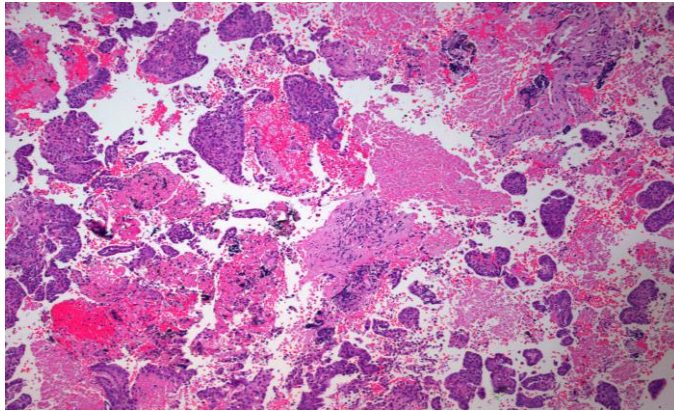


Image 1: Pleural epithelioid mesothelioma: poorly cohesive sheets and clusters of large epithelioid cells with occasional multinucleation (HE). (HE x 100 magnification)

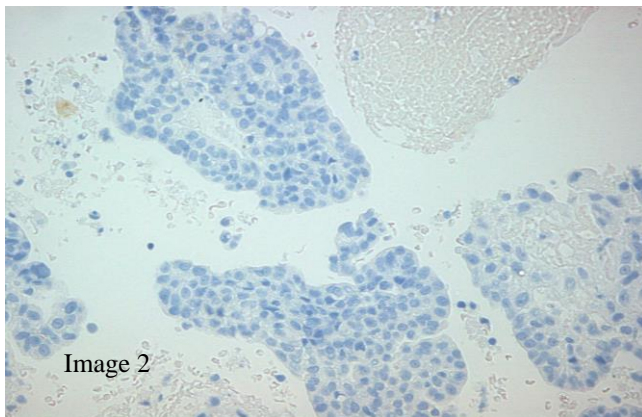


Image 2

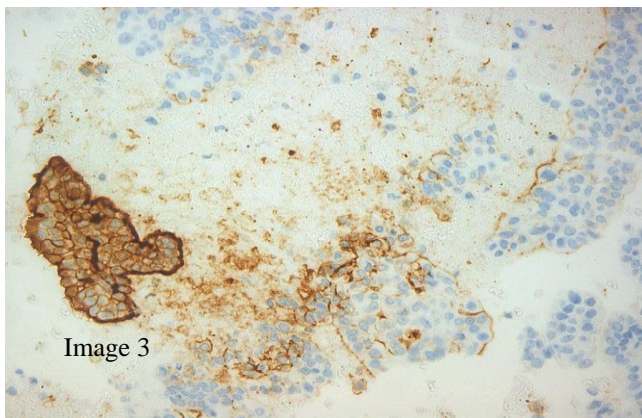


Image 3

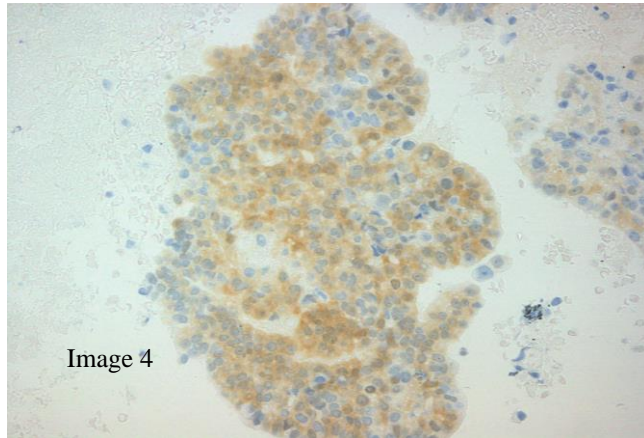


Image 2. Epithelioid mesothelioma: malignant cells are positive for calretinin.

Image 3. Epithelioid mesothelioma: malignant cells are positive for D2-40.

Image 4. BerEP4 (IHC) is negative for mesothelioma.

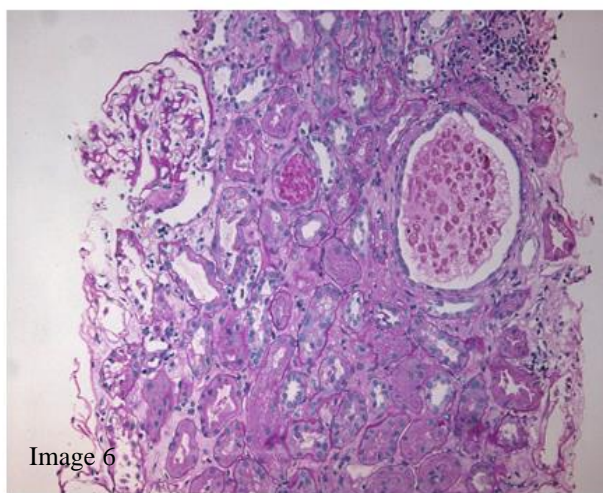
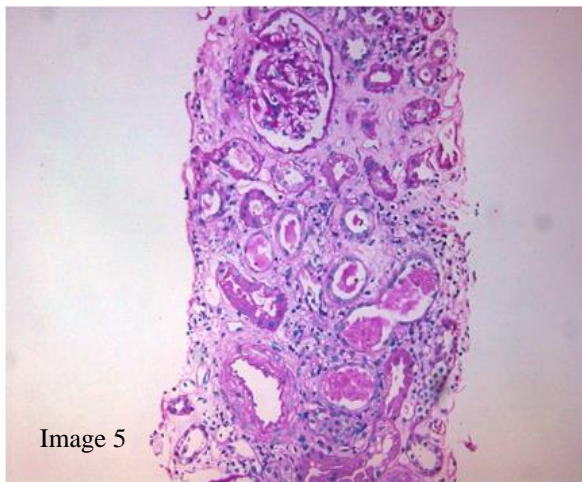


Image 5, 6: Interstitial nephritis with diffuse chronic interstitial lymphocytic infiltrate with occasional eosinophils associated with interstitial fibrosis, tubular atrophy and occasional tubulitis. Glomeruli are unremarkable (PAS Stain x 100 magnification)

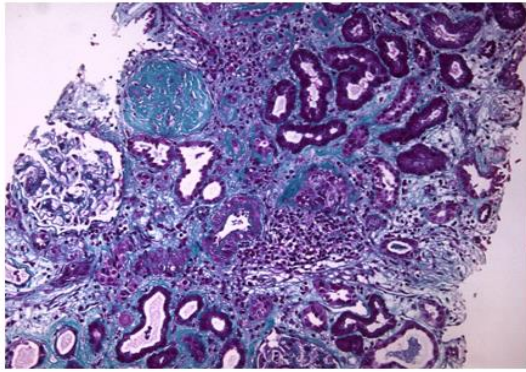


Image 7: Interstitial nephritis with diffuse chronic interstitial lymphocytic infiltrate with occasional eosinophils associated with interstitial fibrosis, tubular atrophy and occasional tubulitis (Masson trichrome x 200 magnification)

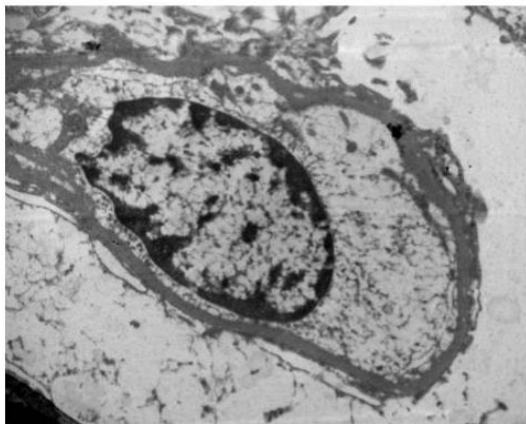


Image 8: Electron microscopy showed extensive foot process fusion consistent with minimal change.

Table 1: MCD, minimal change disease, MGN membranous glomerulopathy

	Age/sex	Type of mesothelioma	Glomerulopathy	Diagnosis of MCD	Diagnosis of MEM	Treatment	Length of survival after diagnosis of MEM
Schroeter et al. (1986)	68, m	Pleura MEM	MCD	8/1983	2/1984	Corticosteroids, CyS	6 m
Venzano et al. (1990)	48,m	Pleura MEM	MGN	n.n	n.n	n.n	n.n
Tanaka et al. (1994)	77,m	Pleura MEM	Prol. Seg. GN	11/1991	12/1991	Corticosteroids, Chemo	5m
Galesic et al. (2000)	67,m	Pleura MEM	MGN	12/1996	11/1997	Corticosteroids	11m
Farmer & Goldsmith (2001)	66,m	Sarcomatous mesothelioma	MCD	12/1997	12/1997	Corticosteroids	15 d
Bacchetta et al.	63,m	Tunica vaginalis	MCD	9/2002	10/2003	Corticosteroids	29 months

(2009)		testis					
Suzuki et al. (2014)	64, m	pleura	MCD	2014, sim	2014, sim	No treatment	11 days
Li et al. (2010)	58, m	pleura	MCD	sim	Sim	Corticosteroids, Chemo	6 weeks
Dogan et al. (2012)	42, f	peritoneum	Refused biopsy	sim	Sim	Chemo, corticosteroids	9 months
Tsukamoto et al. (2015)	73, m	pleura	MCD	13 months after diagnosis	4	Corticosteroids, chemo	17 months
Yildiz et al. (2016)	77,m	pleura	MCD	sim	Sim	Corticosteroids	3 months
Pu et al. (2016)	23,m	pleura	MGN	sim	Sim	Corticosteroids, chemo	2 weeks