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PLEURAL EFFUSION IN GORHAM-STOUT SYNDROME: A CASE REPORT AND A LITERATURE REVIEW

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ABSTRACT

Gorham-Stout syndrome (GSS) is an uncommon disease characterized by massive osteolysis due to bone resorption associated with proliferation of blood or lymphatic vessels. Pleural effusion is an uncommon manifestation. We present a case report of GSS in a 46 year old patient admitted for bilateral serohematic pleural effusion and a review of the literature regarding GSS associated with pleural effusion. We analyzed 48 clinical casesfounded in English language literature concerning pleural effusion secondary to GSS. Patients affected by GSS manifesting pleural effusion are prevalently male with a large range of age. Pleural effusion is more frequently chylous (86%), but it can be also serohematic, transudative or bloody. Direct pleural involvement by the disease has been assessed only in some cases of chylothorax, otherwise the pathological process underlying the liquid production remains unknown. Pleural effusion is most of time bilateral. More frequently it conditions ingravescent dyspnea and when it is chylous it can determine malnutrition. No standard therapy has been established. In patients with relapsing pleural effusion several therapeutic approaches have been used: radiation therapy on mediastinum, pleurodesis, thoracic duct ligation, octreotide administration. Radiation therapy seems to be effective even when applied only on the bone lesions. Bisphosphonates and alpha-2b Interferon are useful to improve the multiple sites of disease, thanks to their systemic action. The papers considered report a short follow up time, during which almost 50% of the treated patients had no recurrences, but more or less 20% of the patients died.

Keywords: Pleural effusion, Gorham-stout syndrome, Pleural disease, Chylothorax, Osteolysis, Treatment strategy.

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Contribution/ Originality

This study contributes to the existing literature by presenting the first case of bilateral serohematic pleural effusion in Gorham-Stout syndrome that was investigated with chest ultrasound and medical thoracoscopy bilaterally. Furthermore, this study provides the first review of clinical cases reporting pleural effusion secondary to Gorham-Stout syndrome.

1. INTRODUCTION

Gorham-Stout syndrome (GSS) is an uncommon disease firstly described by Jackson in 1838 as a clinical condition characterized by massive osteolysis. In 1955 Gorham and Stout refered to this disease as disappearing bone, caused by excessive bone resorption associated with apparently nonmalignant proliferation of blood or lymphatic vessels [1]. This syndrome can develop in males and females of any race and any age, indeed the youngest patient reported is one month old and the oldest one is 75 years old. Clinical presentation is very inconstant, depending on the number and the localization of the lesions. Generally, it is characterized by pain, functional impairment and swelling, but it can be asymptomatic until a pathologic fracture. Radiological features of bone vary from patchy osteoporosis to fractures or complete resorption. Definitve diagnosis is achieved perfoming a histopathological analysis of the lesions that reveals nonmalignant hyperproliferation of small vessels. Although this disease is considered benignant, the prognosis can be very poor. Complications of this disease include pleural effusion, that can seriously impair respiratory function [2]. Few cases are reported about pleural effusion in Gorham-Stout syndrome. We present a case with bilateral serohematic pleural effusion and a revision of the literature regarding GSS associated with pleural effusion. Our intent is to better define the clinical presentation and the prognosis of the patients presenting pleural effusion in GSS, assessing the most successful treatment of this complication.

2. CASE REPORT

A 46 year old man was admitted to our division for bilateral pleural effusion in October 2010. Clinically he claimed ingravescent dyspnea and persistent thoracic pain in correspondence of manubrium lasting for 3 weeks. The patient was treated with Levothyroxin for previous thyroidectomy, performed for papillary thyroid cancer. Blood examination was normal, fever was absent. Chest CT showed abundant bilateral pleural effusions more extended on the left side and compressive lung consolidation at the bases without lymphadenopathies. It was also apparent a lytic lesion of the manubrium sterni involving the first right chondrosternal and the left sternoclavicular joints. Chest ultrasound displayed bilateral complex nonseptated pleural effusion with hematocrit sign (*figure 1*).

Initially we decided to position a right thoracic tube and 2000 ml of serohematic liquid were drained. Cytological examination resulted negative for neoplastic cells. In the next days the tube continued to drain conspicuous pleural liquid, then we decided to perform a medical thoracoscopy

(MT) without pleurodesis on the contralateral side. Parietal pleura appeared diffusely thick and hyperemic, without any other lesions (*figure 2-3*). Every specimen obtained during the pleuroscopy resulted in nonspecific pleural inflammation.

We performed also an ago-biopsy of the osteolytic lesion that revealed only fibrotic areas. Then we executed a positron emission tomography (PET) to look for any other lesions. It confirmed the presence of the known injury of the manubrium without other pathological alterations except for a diffuse pleural enhancement. Since the patient felt better, although all our diagnostic tests resulted not conclusive, he was discharged, waiting before any other further investigations.

Because of perpetual bilateral pleural effusions, after two months we decided to admit another time the patient. The clinical scenario was similar to that one of the previous admission. This time we performed a MT on the right side. The examinations on the specimens obtained results resulted identical to that performed previously. However this time talc poudrage was carried out.

At this stage we were able to exclude any pleural diseases (bilateral MT), a thyroid cancer recurrence or any other primitive cancers (PET), but we could not explain pathological process underlying the osteolytic area of the manubrium. Thus, although the previous ago-biopsy resulted negative, we decided for surgical excision of this lesion. A large biopsy was collected with osseous, cartilaginous and muscular tissue. Microscopic evaluation showed osteolysis areas with proliferation of mainly blood and more rarely lymphatic vessels. A collegial discussion with pathologists let us to reach the correct diagnosis. Considering that the lesion was already totally cut off surgically and that there was no evidence of other localizations, we decided to radicalize the treatment with local radiation therapy. No other treatment was applied.

Radiological and sonographic follow-up showed no recurrence until March 2015 (more than 4 years from the diagnosis), when a chest x-ray showed moderate right pleural effusion and left basal hydropneumothorax associated to 3rd rib irregularity and contiguous soft tissue thickening. Despite these radiological findings, the patient was asymptomatic and no diagnostic investigations or treatment were performed, continuing only follow up.

3. DISCUSSION AND LITERATURE REVIEW

Gorham-Stout syndrome (GSS) is a rare disorder characterized by osteolysis [1]. The typical anatomopathological pattern is bone resorption due to proliferation of blood and lymphatic vessels. It can involve different bones, even with multiple localizations and it can spread to the adjacent tissue. Definitive diagnosis is obtained with histological examination of the lesions that reveals proliferation of blood and lymphatic vessels causing bone resorption. Until now the exact pathogenetic mechanism is not elucidated so it remains an idiopathic disease. Rarely GSS can induce pleural effusion. We reviewed the literature in order to clarify epidemiology, clinical characteristics and therapies of pleural effusion in GSS. We carried out a revision of all clinical cases present in English language literature (Medline Pubmed) regarding pleural effusion

secondary to GSS. Pleural effusion is a very rare presentation in GSS, indeed we founded only 51 clinical cases reported [3-48] 3 ones were excluded from this work because the pleural effusion was presumably secondary to the surgical procedure [42, 47, 48]. Thus this review considers 48 case reports from literature in addition to ours (*table 1*).

Clinical characteristics of the disease are reported in *table 2*. The patients are prevalently male (M:F=34:15); 1 year old the youngest [40] and 63 years old the oldest [10]. Bone lesions are frequently multiple, displaced in different regions of the body (*table 1*). Pleural effusion has almost constantly the typical characteristics of chylothorax (86%), only 5 cases presented serohematic pleural effusions (10%) and in 2 cases pleural effusion was transudative and bloody respectively (*table 2*).

Our analysis of the literature shows that the pathogenesis of pleural effusion in GSS is not yet established. In fact in our clinical case with serohematic pleural effusion, although the GSS lesion involve a bone adjacent to the parietal pleura, bilateral medical thoracoscopies showed only a diffuse non-specific pleural inflammation. Also in the other case of serohematic pleural effusion, studied with thoracotomy, the macroscopic observation and the microscopic analysis of pleura specimens did not display abnormal proliferation of blood vessels, the typical lesions of GSS, but only chronic inflammation [11]. Thus the etiopathogenesis of serohematic pleural effusion production in GSS is not clarified. We can only suppose an indirect involvement of the pleura in the pathological process. In a limited number of cases with chylothorax, lymphangiography showed a disruption of the normal architecture of the thoracic duct that appeared enlarged and convoluted [3, 29]. Moreover in other cases, a proliferation of lymphatic vessels was demonstrated in histological specimens of the pleura [15-18, 22, 26, 29, 31, 39]. Sometimes the bone lesions are localized remote from the chest [7, 16, 21, 39] in these cases the pathogenetic mechanisms of chylothorax is completely unknown and an undefined systemic process damaging the thoracic duct or other lymphatic vessels can be only supposed. Further studies will be needed to elucidate this aspect.

Clinically it resulted that pleural effusion in GSS is most of time localized bilaterally or on the right side (41% and 33% respectively) (*table 2*). Often the symptom at the onset of the disease is represented by ingravescent dyspnea secondary to abundant pleural effusion that limits the lung expansion. Due to the frequent young age of the patients, the peripheral oxyhemoglobin saturation normally is not severely compromised at the beginning. More rarely, GSS with pleural effusion can start with chest pain associated or not with dyspnea (*table 2*). At times, particularly when the pathologic process involves the bones of limbs, a pathological fracture can be the first sign of disease [21]. Most of the time pleural effusion in GSS requests several thoracentesis or a chest drainage inserction by the reason of quick relapses. Even several liters of chylous liquid can be produced in a few days conditioning malnutrition [9, 12, 26, 27, 30, 32]. Frequently this complication necessitates a rapid parenteral nutritional support and human albumin replacement. When pleural effusion is unilateral it can conduce to mediastinal shift if it is not treated promptly

[35]. Considering the little number of cases described to date, there are no standard therapies for pleural effusion caused by Gorham disease. In *table 1* the different treatment and the clinical outcome are scheduled. Our examination of literature suggests that systemic drugs are the most frequent treatment. In particular bisphosphonates and alpha-2b interferon (IFN □-2b) [14] seem to be the most effective because they can control directly the multiple bone lesions. It is known that bisphosphonates modulate osteoclasts activity, that is the most important responsible of the bone resorption. It has been observed that bisphosphonates regulate osteoclastic regulators osteoprotegerin (OPG) and free soluble RANKL serum concentrations [49]. OPG and RANKL have opposite functions, particularly RANKL promotes osteoclasts activity with bone resorption and OPG contrasts the linkage of RANKL with its receptor. During the treatment with bisphosphonates, serum dosages of OPG increase while the level of soluble RANKL drop with an increase of OPG/RANKL ratio and a subsequent imbalance towards osteoblastic activity [50]. Moreover it is known that RANKL expression is stimulated by IL-6 that is considered to be implicated in the pathogenetic mechanism of this disease. Indeed the serum IL-6 levels are elevated in the patients affected by GSS but they decrease after treatment with bisphosphonates [49, 51]. The other drug used in GSS is IFN □-2 because of its anti-angiogenic effect even if the exact mechanism is not completely understood. It has been observed that, although IFN □-2b stimulates the release of IL-6 within a few hours from a single administration [52] when this drug is chronically applied to a patient with GSS it produces a clinical and radiological remission of the bone lesions. Pleural effusion in GSS can be controlled by surgical, medical or radiation approaches and frequently more than one is needed in the same patient. Thoracic duct reconditioning can be achieved by surgical ligation or by diathermy. These procedures should be applied only after a lymphographic study that demonstrates the thoracic duct leakage. In fact, the thoracic duct ligation should be performed only when the site of the leakage of the lymphatic vessel is accurately localized during the surgical procedure. In some cases this surgical management could not be carried out because the seepage is not recognized. An alternative approach consists in the administration of octreotide, a somatostatin synthetic analogue that can seal the lymphatic leakage [53]. This medical strategy can be performed even in absence of the direct localization of the leakage.

Our review demonstrates a large employment of radiation therapy (RT). It can be used on the bone lesions in order to consolidate the weakness of the bone tissue. In fact GSS is frequently related to pathologic fractures. Often this is the first clinical manifestation of the disease. Moreover RT seems to be able to eradicate directly the pathological process contrasting the vessel proliferation. Furthermore it is useful to stop pleural effusion production when it is performed on the mediastinum, probably because it can heal the lymphatic system. In our opinion, this procedure seems to be more successful than the approaches described previously, also considering that it can be performed even without a lymphographic study. Thus a larger number of patient can be treated with RT compared to surgical approaches. Moreover RT can operate on

an extended area; this vantage allows to treat at the same time different areas potentially involved by the disease in the mediastinum. In order to control pleural effusion, pleurodesis can be performed. Several modalities have been founded. The most applied method is the use of talc. Talc poudrage is a standard procedure that can be easily carried out during thoracoscopy or thoracotomy. In our opinion, it is little more favorable than the talc slurry that can be more easily performed injecting a dispersion of talc in a sterile normotonic saline solution through a chest drainage. In our experience, we performed a talc poudrage during MT on a single side with good results. Other Authors proposed to use a relatively new drug: Picibanil, also called OK-432. It is a lyophilized mixture of group A Streptococcus pyogenes: like talc it should be able to produce pleurodesis eliciting fibrosis. Instead, the surgical approach is represented by pleural decortication that is obviously characterized by larger complications. In this case we are not able to indicate the best modality.

Finally, when the lesion is single and early diagnosed, a surgical excision can be performed. This way can be useful even to obtain the diagnosis, like in our experience. Moreover, we believe that the use of steroid in these patients is controversial; to date we are not able to understand the pathogenic mechanism of its employment.

In the case reports considered mean follow up time was limited to 2.0 years (SD ± 1.86). It is important to underline that clinical outcome was not specified in all papers. However, focusing only on the available data it resulted that almost 2/3 patients had no recurrences after the treatment, but more or less 30% of the patients died despite the clinical effort. The ingravescence of the disease is documented only in 2 cases.

4. CONCLUSION

Our review about the cases of GSS with a pleural involvement suggests that the treatment options are various. Frequently they need to be associated in a multimodality approach. Moreover the clinical scenarios are very heterogeneous with a large range of age and a large variability of symptoms. The little number and the variability of the cases reported prevent to identify a widely approved therapeutic strategy. This is a very serious disease caracterized by a poor prognosis in 1/3 patients, thus it is important to achieve the diagnosis quickly, starting the most suited treatment for the patient.

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Table-1. Summary of the clinical cases present in literature.

Case	Date	Age	Sex	Bone localization	Diagnostic approach	Treatment	Clinical outcome
Patrick JH [4]	1976	28	M	Multiple	Bone biopsy	RT, decortication, thoracic duct coagulation, pleurodesis	NR (1 yr)
Feigl D et Al [5,6]	1981	26	F	Clavicle	Bone biopsy, thoracoscopy	Surgical, talc pleurodesis	NR (8 yrs)
Brown LR at Al [7]	1986	30	M	Multiple	Thoracotomy	TDL	Died quickly
Heigaard N et Al [8]	1987	9	M	Multiple	Bone biopsy	Pleurodesis	NR
Mitchell CS et Al [9]	1993	16	F	Sternum and ribs	Bone biopsy	Surgical	
Tie ML et Al [10]	1994	30	M	Multiple	Bone biopsy	Pleurodesis, RT, decortication	Died quickly
Tie ML et Al [10]	1994	18	M	Multiple	Bone biopsy	Decortication, TDL	NR (2 yrs)
Ng SE et Al [11]	1995	63	F	Multiple		Thoracentesis	Died for MI
McNeil KD et Al [12]	1996	21	M	Multiple	Thoracotomy, bone biopsy	RT	NR (4 yrs)
Riantawan P et Al [13]	1996	27	M	Multiple	Necroscopic		Died quickly
Aoki M et Al [14]	1996	19	F	Vertebrae	Bone biopsy	RT, pleurodesis with Minocycline and Bleomycin	NR (2 yrs)
Hagberg H et Al[15]	1997	19	M	Vertebrae	Bone biopsy, CT chest	Bps, IFN	NR (19 mos)
Podevin G et Al [16]	1999	4	M	Multiple	Thoracotomy	Pleurectomy, TDL, pleuro-peritoneal shunt	NR (15 mos)
Chavanis N et Al [17]	2001	45	F	Left upper limb	Radiological	TDL, pleurectomy, talc pleurodesis	NR (1 yr)
Miller GG [18]	2001	2	M	Multiple	Thoracotomy	TDL, pleurectomy	Died (2 yrs AD)
Fujiu K et Al [19]	2002	15	M	Multiple	Bone biopsy, VATS	TDL	Died
Yoo SY et Al [20]	2002	38	M	Multiple	Mediastinal biopsy	RT	
Lee WS et Al [21]	2002	25	F	Ribs, vertebras	Bone biopsy, thoracoscopy	Pleurodesis with OK-432, RT	Little progression (20 mos)
Fontanesi J [22]	2003	21	M	Homerus	Radiological	RT	NR (6 mos)
Swelstad MR et Al [23]	2003	31	F	Multiple	Bone biopsy	Pleurodesis, RT	
Kren L et Al [24]	2005	7	M	Multiple	Bone biopsy	Pleurodesis with pleurectomy and talc	
Takahashi A et Al [25]	2005	2	F	Multiple	Thoracoscopy	OK-432, IFN and steroid	NR (10 mos)
Duffy B et Al [26]	2005	31	F	Multiple	Bone biopsy	Talc pleurodesis, RT, steroid	NR (3 yrs)
Pfleger A et Al [27]	2006	18	M	Multiple	Spleen biopsy, thoracotomy	IFN, BPs, OT, pleurodesis	NR (12 mos)
Underwood J et Al [28]	2006	47	M	Clavicle	Unknown	TDL	
Hagendoom J et Al [29]	2006	17	M	Multiple	Bone biopsy, thoracotomy	Thal, IFN, BPs, pleurectomy, talc pleurodesis, Imatinib	Died (46 mos AD)
Vigorita VJ et Al [30]	2006	35	M	Multiple	Bone biopsy	Thoracentesis	Died quickly
Boyle MJ et Al [31]	2008	17	M	Multiple	Bone biopsy	Pleurodesis, TDL, RT	Died quickly
Kose M et Al [32]	2009	7	F	Multiple	Thoracotomy	Steroid, TDL, RT, pleural-peritoneal shunt, IFN	NR (6 mos)
Yildiz TS et Al [33]	2009	6	M	Thoracic cage	Parietal chest biopsies	TDL	
Kuriyama DK et Al [34]	2010	16	F	Multiple	Bone and chest wall biopsies	IFN, BPs	NR (2 yrs)
Seok YK et Al [35]	2010	14	M	Ribs and T7	Thoracotomy	TDL, RT	NR (5 mos)
De Smet K et Al [36]	2010	8	M	Multiple	CT chest, bone biopsy	Somatostatin, steroid, clipping thoracic duct, BPs, IFN	NR (8 mos)
Deveci M et Al [37]	2011	6	M	Multiple	Bone biopsy	TDL, pleurectomy, IFN, BPs	Died (4 mos AD)
Brodszky N et Al [38]	2011	2	M	Multiple	Bone surgical biopsy	IFN, Bev, OT, RT, PL, TDL, pleurodesis	NR (2 yrs)
Brodszky N et Al [38]	2011	4	F	Multiple	Pleural and bone biopsies	IFN, RT	NR (3 mos)
Zheng MW et Al [39]	2012	5	F	Multiple	Bone biopsy	BPs	NR (3 yrs)
Kotecha R et Al [40]	2012	14	M	Multiple			
Kotecha R et Al [40]	2012	13	F	Multiple			
Kotecha R et Al [40]	2012	12	M	Multiple			
Kotecha R et Al [40]	2012	9	F	Multiple			
Hopman S et Al [41]	2012	1	M	Multiple	Chest wall biopsy	IFN	Died (1 yr AD)
Noda M et Al [42]	2013	15	M	Spine C1-C8	Bone biopsy	IFN, OT, TDL, pleurodesis with OK-432, RT	Multiple recurrences
Barman A et Al [43]	2013	23	M	Multiple	Known diagnosis	Thoracentesis	NR (4 mos)
Chen B et Al [44]	2013	8	M	Multiple	Bone biopsy	RT	NR
Choi BS et Al [45]	2014	13	M	Multiple	L2 biopsy	Pleurodesis	
Ozcan R et Al [46]	2014	7	M	Multiple	Thorax MRI	Somatostatin, steroid, IFN	NR (2 yrs)
Daneshvar KA et Al[47]	2014	48	M	Multiple	Bone biopsy	TDL, RT, BPs, Thal	NR (7 yrs)
Current study	2015	46	M	Manubrium	MT and bone biopsy	Surgical, talc pleurodesis, RT	NR (3 yrs)

Abbreviations: Treatment: RT: radiotherapy, IFN: Interferon α-2b; BPs: Bisphosphonates, TDL: thoracic duct ligation, Bev: Bevacizumab, OT: Octreotide, OK-432: Picibanil, Thal: Thalidomide, PL: pulmonary lobectomy; Clinical outcome: NR: No recurrence, MI: myocardial infarction, yr/yrs: year/years, mos: months, AD: after the diagnosis.

Table-2. Clinical characteristics of the disease.

Age (mean ± SD)	19.1	± 14.18
Gender	n.	%
Male	34	69.4
Female	15	30.6
Clinical presentation	n.	%
Dyspnea[4,5,8-13,16,18,20,21,23,24,26-28,31-33,35,37,41-43,45]	31	72.1
Chest pain[4,9,10,12,22,23,29,31,34]	13	30.2
Other pain[14,30,32,38,39,42]	6	14.0
Fever[27,30,32]	4	9.3
Asymptomatic pleural effusion[7,25,38]	3	7.0
Types of pleural effusion	n.	%
Chylous[4,7,8,10,13,14,16-38,40-47]	42	85.7
Serohematic[9,11,12]	5	10.2
Trasudate[39]	1	2.0
Bloody[5]	1	2.0
Side	n.	%
Bilateral[5,7-9,10,13,14,19,25,26,30,33,37,38,40,43]	20	40.8
Right[8,11,12,18,21-23,27,28,32,35,38,40-42]	16	32.7
Left[4,10,16,17,20,24,31,34,36,39,45]	13	26.5
Outcome	n.	%
No recurrence	25	51.0
Progression	2	4.1
Died	10	20.4
Not specify	12	24.5
Mean follow-up time (yrs ± SD)	2.0	± 1.87

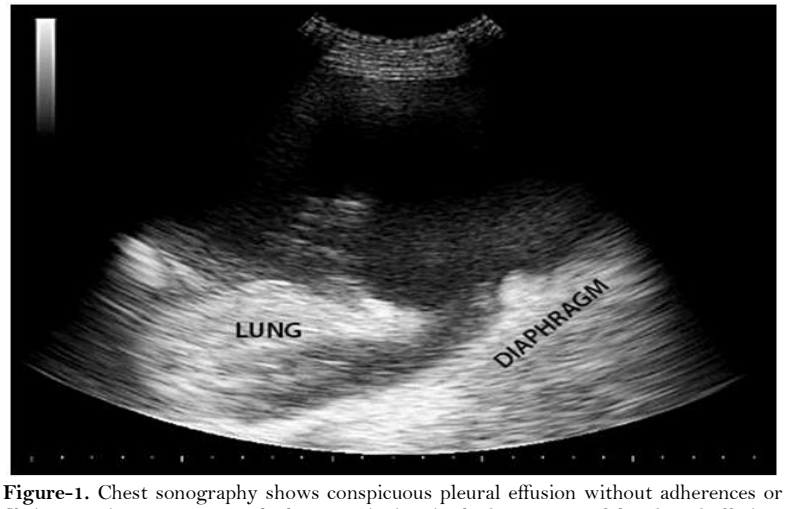

Figure-1. Chest sonography shows conspicuous pleural effusion without adherences or fibrin septations. It presents the hematocrit sign: in the lower zone of the pleural effusion, upon the diaphragm and the lung, an area weakly hyperechoic can be appreciated. The lung appears collapsed by pleural effusion compression.

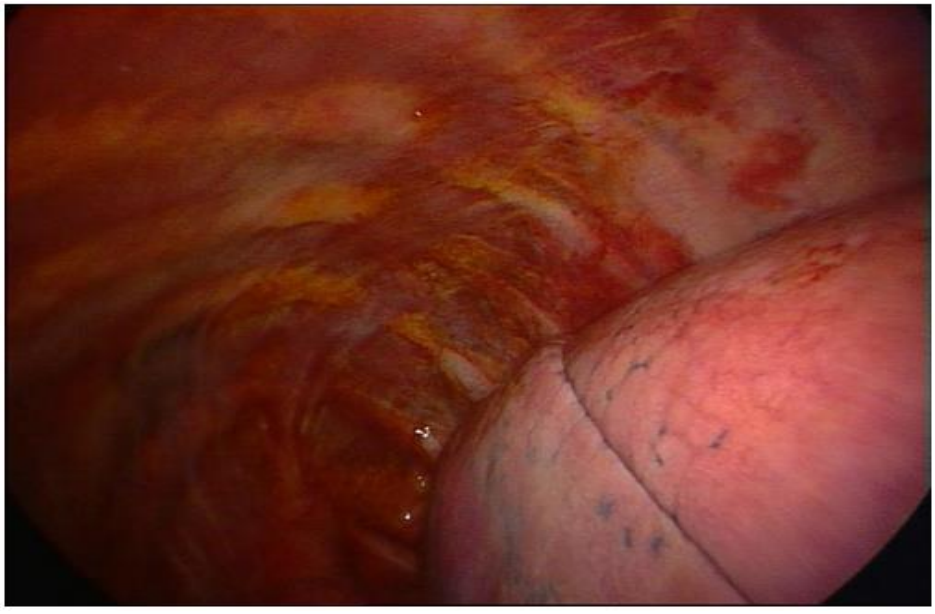

Figure-2. Endoscopic picture during medical thoracoscopy. On the right the lung with the major fissure, no macroscopic alteration can be seen. All around the chest wall with the ribs. Parietal pleura is extensively thickened and hyperemic.

Figure-3. Endoscopic picture during medical thoracoscopy. Close-up of hyperemic parietal pleura.