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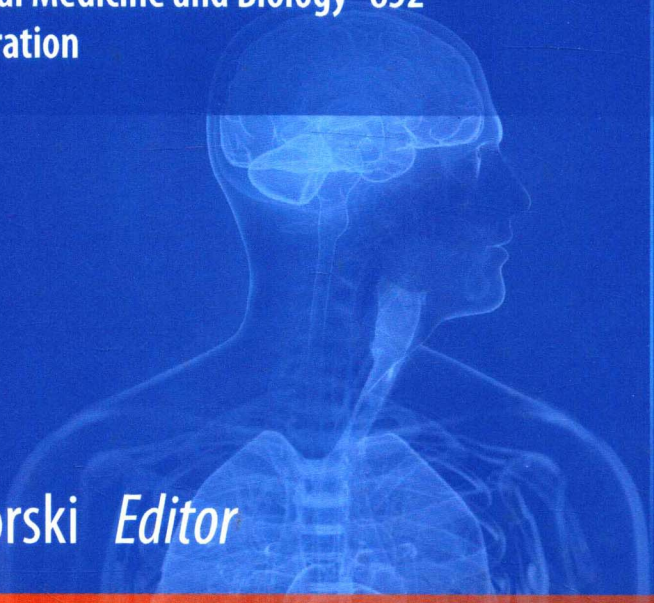
Neuroscience and Respiration



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Respiratory Carcinogenesis

Springer

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Preface

The book series *Neuroscience and Respiration* presents contributions by expert researchers and clinicians in the field of pulmonary disorders. The chapters provide timely overviews of contentious issues or recent advances in the diagnosis, classification, and treatment of the entire range of pulmonary disorders, both acute and chronic. The texts are thought as a merger of basic and clinical research dealing with respiratory medicine, neural and chemical regulation of respiration, and the interactive relationship between respiration and other neurobiological systems such as cardiovascular function or the mind-to-body connection. The authors focus on the leading-edge therapeutic concepts, methodologies, and innovative treatments. Pharmacotherapy is always in the focus of respiratory research. The action and pharmacology of existing drugs and the development and evaluation of new agents are the heady area of research. Practical, data-driven options to manage patients will be considered. New research is presented regarding older drugs, performed from a modern perspective or from a different pharmacotherapeutic angle. The introduction of new drugs and treatment approaches in both adults and children also is discussed.

Lung ventilation is ultimately driven by the brain. However, neuropsychological aspects of respiratory disorders are still mostly a matter of conjecture. After decades of misunderstanding and neglect, emotions have been rediscovered as a powerful modifier or even the probable cause of various somatic disorders. Today, the link between stress and respiratory health is undeniable. Scientists accept a powerful psychological connection that can directly affect our quality of life and health span. Psychological approaches, by decreasing stress, can play a major role in the development and therapy of respiratory diseases.

Neuromolecular aspects relating to gene polymorphism and epigenesis, involving both heritable changes in the nucleotide sequence and functionally relevant changes to the genome that do not involve a change in the nucleotide sequence leading to respiratory disorders, will also be tackled. Clinical advances stemming from molecular and biochemical research are but possible if the research findings are translated into diagnostic tools, therapeutic procedures, and education, effectively reaching physicians and patients. All that cannot be achieved without a multidisciplinary, collaborative, bench-to-bedside approach involving both researchers and clinicians.

The societal and economic burden of respiratory ailments has been on the rise worldwide leading to disabilities and shortening of life span. COPD alone causes more than three million deaths globally each year. Concerted efforts are required to improve this situation, and part of those efforts are gaining insights into the underlying mechanisms of disease and staying abreast with the latest developments in diagnosis and treatment regimens. It is hoped that the books published in this series will assume a leading role in the field of respiratory medicine and research and will become a source of reference and inspiration for future research ideas.

I would like to express my deep gratitude to Martijn Roelandse and Tanja Koppejan from Springer's Life Sciences Department for their genuine interest in making this scientific endeavor come through and in the expert management of the production of this novel book series.

Opole, Poland Mieczyslaw Pokorski

Volume 11: Respiratory Carcinogenesis

The book blends basic and clinical research on respiratory carcinogensis. The contributions tackle a variety of respiratory-related cancers, notably non-small cell lung carcinoma, pleural mesothelioma, mediastinal tumors, or larynx cancer. The focus is on the search for novel molecular markers, derived from easily accessible tissues in clinical settings, such as the serum or bronchoalveolar lavage fluid, which could help diagnose cancer at an early stage and have a prognostic therapeutic value. The transcriptional mechanisms which endow cells with the capacity for unlimited proliferation are considered, with silencing of tumor suppressor genes is the exemplar. Chapters provide insight into a variety of cancer-related disorders of the respiratory tract, novel ways of differential diagnosis and treatment. The aim is to bring the current clinical procedures into alignment with the latest basic research findings. The book is a text for respiratory researchers, clinicians, and pathologists.

Contents

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The Role of Mediastinoscopy in the Diagnosis of Thoracic Disease: One-Year Single Center Experience

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Abstract

Our experience of using mediastinoscopy for the diagnosis of enlarged mediastinal lymph nodes or mediastinal mass is presented in this study. We reviewed 54 consecutive patients (34 men and 20 women) with mediastinal pathology of varied etiologies who underwent a standard cervical mediastinoscopy from January to December 2012. The histological results were positive in 32 cases (59.2 %), and negative in 22 cases (40.8 %). Transient laryngeal recurrent nerve palsy manifested as prolonged hoarseness of voice was the only minor complication in 3 cases (5.5 %). The sensitivity of the procedure was 72 %, and the specificity was 100 %. We recommend the use of a mediastinoscopy in the staging of lung cancer and the diagnosis of mediastinal mass when other non-invasive procedures are ineffective.

Keywords

Lung cancer • Lymphoma • Mediastinoscopy • Staging • Sarcoidosis

1 Introduction

The standard cervical mediastinoscopy (SCM) was first described by Carlens (1959). This procedure is considered an invasive but safe method for the initial staging of lung cancer, for the diagnosis of mediastinal tumors or granulomatous diseases, i.e. tuberculosis and sarcoidosis (Fibla et al. 2006). Mediastinoscopy is associated with a relatively low postoperative morbidity rate and occasional mortality. The complications include hemorrhage, pneumothorax, recurrent laryngeal nerve injury, esophageal and tracheal perforation, and wound infection (Elsayed 2012; Dunning and Walker 2012). There is little data in the literature reporting the extent to which the surgeon's experience or the implementation of the technique influences the results (Walles et al. 2013).

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2 Methods

The protocol of the study was approved by a local Ethics Committee. We conducted a retrospective single-centre analysis of the records of patients who had undergone mediastinoscopy in our Surgical Department over a 1-year period. The aim of the study was to determine the safety, efficacy, and the current role of mediastinoscopy in the evaluation of mediastinal disease. The diagnostic evaluation included a conventional workup (medical history, physical examination, laboratory tests, and bronchoscopy). All the patients also had preoperative computerized tomography (CT) scans performed. Patients with radiological enlarged mediastinal lymph nodes (diameter >1 cm) or mediastinal masses were subjected to a diagnostic mediastinoscopy. A standard cervical video-assisted mediastinoscopy was performed without an immediate frozen section. General anesthesia and intubation with a single-lumen tube was employed. Patients were in the dorsal decubitus position with a roll under the shoulders. After a transverse cervicotomy, the paratracheal fascia was opened and a blunt finger dissection was done. A spreadable mediastinoscope from Richard Wolf GmbH (Knittlingen, Germany) was inserted. Specimens from lymph node stations 2, 3, 4, and 7 were obtained, the lymph node stations having been classified according to Naruke mediastinal map (Naruke 1993; Naruke et al. 1978). Minor hemorrhaging was successfully controlled by coagulation or gauze packing. The procedures were performed by two consultants in thoracic surgery (MCh and JS). The mortality, morbidity, and sensitivity and specificity of mediastinoscopy for the diagnosis of mediastinal pathology were analyzed. Microsoft Excel XP was used for data collection and basic statistical analysis.

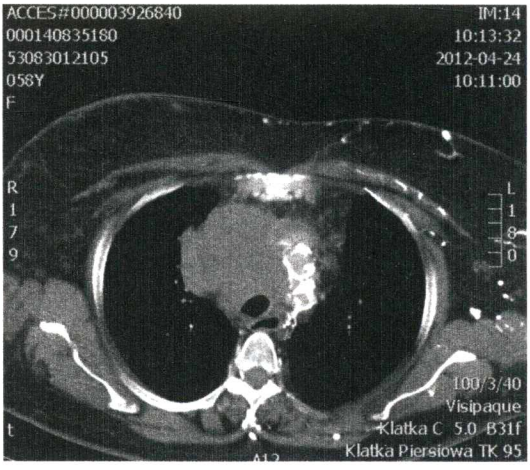

Fig. 1 CT scan showing a large mediastinal mass, which is invading the aortic arch, compressing the right lung parenchyma, and constricting the trachea and the esophagus

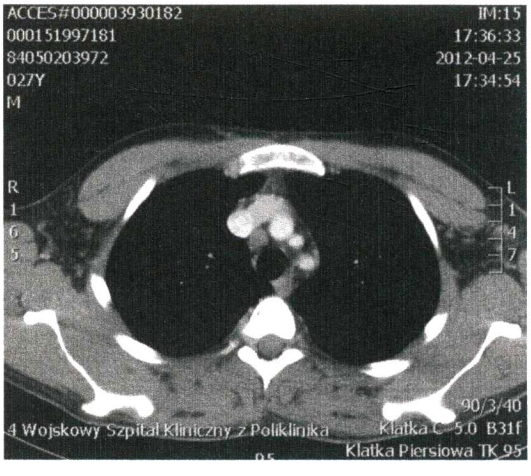

Fig. 2 CT scan showing an enlarged right upper paratracheal lymph node (station 2R)

3 Results

Fifty four patients who underwent video-assisted cervical mediastinoscopy within a 1 year period were enrolled in the study. The study population comprised of 34 men (63 %) and 20 women (37 %), with a median age of 63.5 years (range 25–85). On average 2.5 lymph node stations per patient were reached with each mediastinoscopy.

Mediastinoscopy established a diagnosis in 32 cases (59.2 %): non-small cell lung cancer (NSCLC) (squamous cell carcinoma or adenocarcinoma) in ten patients, small cell lung cancer (SCLC) in 2 (Fig. 1), sarcoidosis in eleven (Fig. 2), B-cell lymphoma in two (Fig. 3), thymic

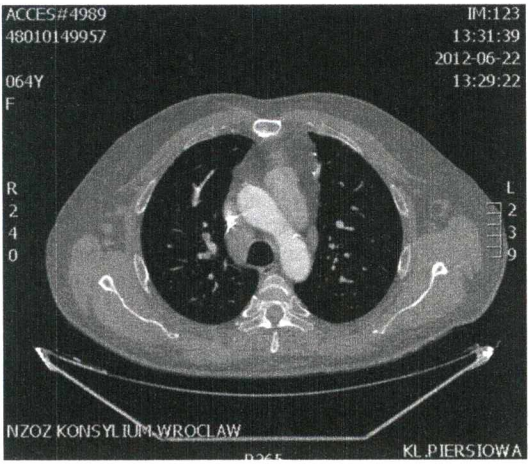

Fig. 3 CT scan showing an enlarged right lower paratracheal lymph node (station 4R)

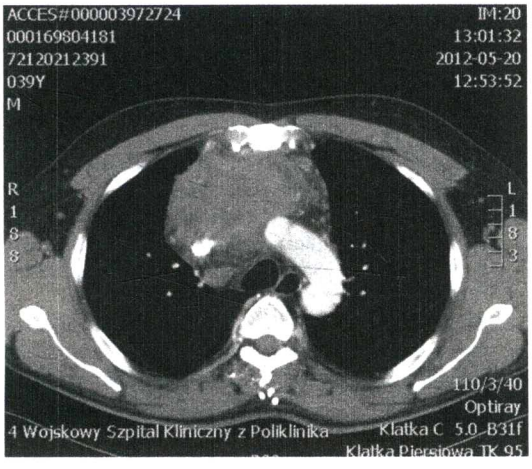

Fig. 4 CT scan showing a large tumor in the anterior mediastinum, which is invading the posterior wall of the sternum and aortic arch, compressing the right and left lung parenchyma, and constricting the trachea

pathology (cancer or thymoma) in four (Fig. 4), and metastases (breast or large bowel cancer) in three.

Negative histological results of mediastinoscopy were obtained in 22 cases (40.8 %). Ten patients did not develop any serious disease, which was confirmed by a positron emission tomography (PET) scans, CT scans, or by further observation (true negative values). Three of these 10 patients underwent a thoracotomy with lymphadenectomy, which proved to be negative. However, 12 patients were discovered to have disseminated cancer, which was confirmed by other diagnostic procedures (false negative values). In our series, the sensitivity of the procedure was 72 %, and the specificity was 100 %.

There were no major complications such as hemorrhaging from major blood vessels. The only minor complication was recurrent laryngeal nerve injury, manifested as prolonged hoarseness of voice, which occurred in three cases (5.5 %). There were no perioperative deaths.

4 Discussion

The role of mediastinoscopy in the evaluation of thoracic disease still remains a debatable subject. Radiological images often do not provide information about the nature of these lesions and consequently fail to enable therapeutic decisions. Surgical exploration of the mediastinum provides a definitive diagnosis as it allows biopsies of lymph nodes or tumors affecting the mediastinum.

The most important question is whether patients with NSCLC will benefit from surgery (Leschber et al. 2008). Mediastinal lymph node involvement (N2 disease), confirming systemic disease, is considered a contraindication for surgery in NSCLC. Mediastinoscopy can obviate an unnecessary thoracotomy. Thoracic CT and PET-CT scans have been widely used for noninvasive tumor staging. Studies have suggested that PET could reduce the need for mediastinoscopy (Hammoud et al. 1999; Vansteenkiste et al. 1998). Invasive mediastinal staging is still necessary as it is based on tissue confirmation. The sensitivity of mediastinoscopy varies between 79 and 93 % (McManus et al. 2008; Fibla et al. 2006). In our series the sensitivity was 72 %. Recently, transbronchial lymph node biopsy by endobronchial ultrasound has been introduced with an approximately 85 % level of sensitivity. The addition of endoscopic ultrasound with fine needle aspiration (EUS-FNA) to mediastinoscopy can increase the sensitivity of detection of mediastinal disease to 93 % (Annema et al. 2010; Annema and Rabe 2006). However, international guidelines regard

the surgical staging as the gold standard. It is suggested that endosonography should be followed by mediastinoscopy if no metastases are found (Annema et al. 2010).

The procedure is safe with minimal morbidity. We noticed only three cases of recurrent laryngeal palsy in our series. However, hemorrhage, vocal cord dysfunction, tracheal injury, pneumothorax, and vascular injury are other major complications that have been described in literature (Chauchan et al. 2012; Minowa et al. 2011; Iskender et al. 2011).

5 Conclusion

Mediastinoscopy, given its safety and efficacy, should be routinely used for the evaluation of mediastinal pathology. The safety of mediastinoscopy safety depends on the experience of the thoracic surgeon. The video-assisted technique allows bi-manual working and improves the efficacy of this procedure.

Conflict of Interests The authors declared no conflicts of interest in relation to this article.

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Shoulder Ring Complaints as a Rare First Symptom of Malignant Pleural Mesothelioma

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Abstract

The prevalence of malignant pleural mesothelioma is often encountered in the areas highly exposed to asbestos. The aim of this paper was a retrospective analysis of shoulder pain as a rare, first symptom of pleural mesothelioma, which constitutes an interdisciplinary diagnostic problem concerning both orthopedics and pulmonology. The research was based on a retrospective review of the patients' medical records. The considered period of time included the years 2006–2012. The study group included a total of 49 patients. Seven patients (14.3 %) presented a complain of shoulder pain, as the first symptom of mesothelioma. The remaining 42 mesothelioma patients, without this symptom, constituted a reference group. The intensity of shoulder pain was, on average, 4/10 on an analog scale. A concomitant limitation of mobility was observed in five out of the seven subjects. In one case, limitation of motion and dysfunction of the shoulder joint were at an advanced stage. Neuralgia of upper limbs was found in two cases. We conclude that shoulder pain may be a manifesting symptom of malignant pleural mesothelioma. The neoplasm appears to have a pleiotropic effect on human body, reflected in different ways of its primary manifestation which may also include the motor system.

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Keywords
Asbestos • Environmental exposure • Pleural malignancies • Pulmonology • Orthopedics

1 Introduction

The incidence of mesothelioma reaches 20/1,000,000 people. However, the estimates are variable as the standardized mortality rate from mesothelioma in the years 1994–2008 was 4.9/1,000,000 people, which makes it even a rarer neoplasm. There also are differences among countries concerning the incidence of mesothelioma (Opitz 2014). It is estimated that about 39,000 cases in the countries of Russia, Kazakhstan, China, India, and Thailand have not been reported, which suggests that the available data may not be up to date (Park et al. 2011). It is known that, in general, the incidence of mesothelioma has an upward trend (Carbone et al. 2012; Robinson 2012) and men are more often affected than women (3.6:1.0) (Delgermaa et al. 2011). Pleural mesothelioma, along with lung cancer and other pleural diseases, is lined to asbestos exposure (Konieczko et al. 2013; Carbone et al. 2012; Skammeritz et al. 2011). There were 4,253 cases of asbestos-linked diseases reported in Poland in the years 1974–2010; pleural mesothelioma was 6.4 % of them (Szeszenia-Dabrowska et al. 2011). Although medicine is still looking for an effective method of treatment, the prognosis in this neoplasm is bad. The survival is about 1 year, despite the application of different methods of treatment - chemotherapy, radiotherapy, aggressive surgical treatment, or phototherapy (Weder and Opitz 2012; Aziz et al. 2002). There are also articles on autoimmune phenomena that arise in response to asbestos exposure (Lee et al. 2014; Pfau et al. 2014) and later accompany pleural mesothelioma if it develops. That is why immune-modulatory drugs have also been tried.

There are a number of non-specific symptoms that accompany mesothelioma. The most frequent are the following: chest pain, dyspnea, cough, weight loss, hyperhidrosis, or fever. Some of them are caused by hydrothorax (NCCN 2013; Mott 2012). Due to the non-specific or asymptomatic course the disease runs, particularly at the beginning stage, it is often detected too late for an effective treatment. It is rather rare when a presaging symptom, like shoulder ring pain, on which this article focuses, can be observed. So far, only two articles have been written, describing single cases of such pain (Verpeut et al. 1999; Mazel and Roolvink 1997). The present study focuses, retrospectively, on describing pleural mesothelioma as one of the shoulder ring pain causes, which should alert diagnostic attention of orthopedicians, patients may sick help from, in this basically pulmonary disease.

2 Methods

The study was accepted by an institutional Review Board for Human Research and was performed in accord with the Declaration of Helsinki for Medical Research Involving Human Subjects. The records of patients with pleural mesothelioma diagnosed over the years 2006–2012 were reviewed. All patients came from the Szczucin municipality in Poland, an area consisting of a population of about 14,000 inhabitants and of known increased risk for environmental asbestos exposure due to the presence of an asbestos-cement establishment. The patients were living in the area for at least

15 years. Seven patients (4 women and 3 men; mean age 51 ± 10, range 41–66 years) who visited orthopedicians because of shoulder ring pain were assessed. A reference group consisted of 42 patients (25 women and 17 men; mean age 64 ± 12, range 38–86 years) with pleural mesothelioma, without any pain in the area of the motor system at the moment of medical consultation. One patient of the seven with the shoulder ring pain and six patients of the reference group were workers at the local asbestos-cement establishment. The shoulder ring pain was diagnosed on the right side in three and on the left side in four patients. Initially, pleura only on one side of the chest was affected. Four of the patients were smoking cigarettes for at least a few years. Two patients presenting with the shoulder ring pain also suffered from asbestosis and Hodgkin's lymphoma.

Chest X-rays and, if necessary, ultrasonography and computerized tomography were used for initial diagnostics. Furthermore, thoracentesis and bronchoscopy were carried out in each case. An average pleural tap amounted to 2,093 ml (range 500–4,600 ml) of fluid in the shoulder ring pain group and 1,250 ml (range 200–3,700 ml) in the reference group. All mesothelioma cases were histopathologically confirmed. Radiograms of two patients presenting with shoulder ring pain are exemplified in Figs. 1 and 2.

After the initial diagnostics at a regional hospital, further treatment took place at the Thoracic Surgery Clinics in the cities of Cracow and Zakopane in Poland. Surgeries of different extend were made, from thoracoscopy with biopsy up to lung resection. Chemotherapy was part of standard treatment. In the shoulder ring pain group videothoracoscopy was carried out in four patients, thoracotomy in two, chemical pleurodesis in three, and pleuropneumonectomy with partial resection of the diaphragm and pericardium in another two patients. In six cases, chemotherapy, involving cisplatin, pemetrexed, or adriablastin, and in three cases radiotherapy were used.

Overall, cancer dissemination was found after a few months in all mesothelioma patients

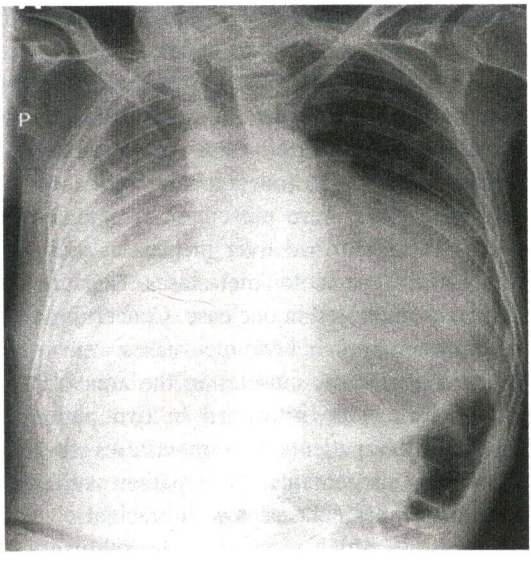

Fig. 1 Chest radiogram of a patient with pleural mesothelioma in the anterior-posterior projection. The examination confirmed hydrothorax on the right side up to the fourth rib, thickened parietal rib pleura and parietal mediastinum pleura. Cardiac silhouette is enlarged with pericardial effusion – neoplastic infiltration of pericardium. Reflexive left bend of the spinal axis due to shoulder ring pain

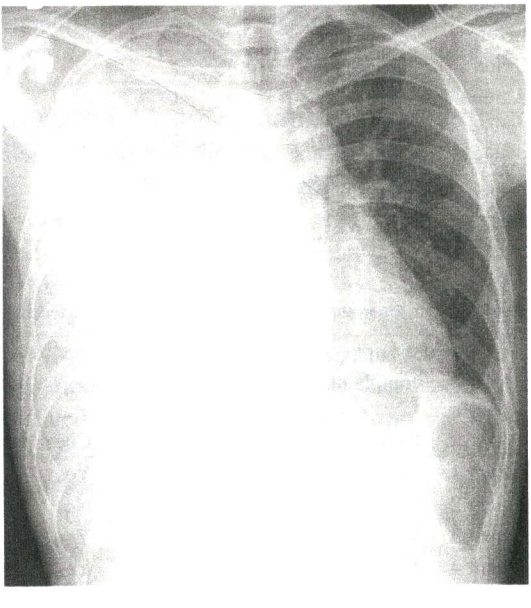

Fig. 2 Chest radiogram of a patient with pleural mesothelioma in the anterior-posterior projection. Right lung completely shadowed by accumulating fluid

presenting with shoulder ring pain. Metastases to the second lung were found in five cases. In two cases, neoplasmatic infiltration of the mediastinum was confirmed, including one patient with an additional infiltration of the esophagus. Metastases to the peritoneal cavity, with accompanying ascites, were present in two patients. One of them also had liver metastases and the other had liver and colon metastases. The adrenal gland was infiltrated in one case. Concerning the motor system, pelvic bone metastases were confirmed in one case, muscles in the area of the pelvic girdle were infiltrated in two patients. Three of the patients had metastases to the abdominal integuments. One patient suffered from the armpit metastases with brachial plexus compression, which resulted in the subluxation of the shoulder joint. The location of metastases is summarized in Table 1. The neoplasm progression and dissemination also were found in the reference group, although it was mostly limited to the lung and pleura on the other side.

Table 1 Metastases in mesothelioma patients with shoulder ring pain

Localization	Number of patients
Lung on the other side	2
Mediastinum	2
Esophagus	1
Peritoneal cavity	2
Liver	2
Colon	1
Adrenal glands	1
Pelvis	1
Pelvis muscles	2
Abdominal integuments	3
Armpit	1

3 Results

The shoulder pain was a presenting complain in all seven patients and made them see an orthopedician. The pain was characterized as diffuse, radiating to the scapula or the neck. Its intensity was rated between 3 and 6 on an analog pain scale, where 0 was no pain and 10 denoted unbearable pain. Three patients rated the pain intensity at 3 points, three other at 4 points, and one at 6 points. Five patients suffered from reduced mobility of the shoulder ring, which was confirmed in physical examination. In one case, the mobility limitation and shoulder joint dysfunction were significant. The ulnar nerve neuralgia of the upper limb was found in two patients; with an additional involvement of the medial and radial nerves in one of them. The following accompanying symptoms were found during the initial work-up: chest pain (5 cases), dyspnea (4 cases), cough (4 cases), weight loss (2 cases), appetite loss (2 cases), and fatigue (3 cases). The exact distribution of symptoms is shown in Table 2. Physical examination showed a pain-related left bend of the spinal axis in one patient, which was confirmed by chest X-ray (Fig. 1). The average survival time, from the time of diagnosis, of the patients with the shoulder ring involvement was 25.4 months (range 12–48 months).

Table 2 Motor system and other symptoms reported to the orthopedician during the initial work-up

	Shoulder ring complaints				Other complaints				
	Pain	Limited mobility	Upper limb neuralgia	Chest pain	Dyspnea	Cough	Weight loss	Appetite loss	Fatigue
Patient 1	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Patient 2	Yes	No	No	No	Yes	Yes	Yes	Yes	No
Patient 3	Yes	Yes	No	Yes	Yes	Yes	No	No	No
Patient 4	Yes	Yes	No	Yes	No	Yes	No	No	Yes
Patient 5	Yes	No	Yes	No	Yes	No	No	No	No
Patient 6	Yes	Yes	Yes	Yes	No	No	No	No	No
Patient 7	Yes	Yes	No	Yes	Yes	No	No	No	Yes

In all 42 patients of the reference group, no complaints connected with the motor system, and especially with the shoulder ring, were reported. In that group, the first symptoms of pleura mesothelioma were the chest pain on the side of infiltration and dry cough. Thirty one of those patients reported dyspnea and fatigue, and six suffered from significant appetite and weight loss. The average survival time in this group was 15.4 months (range 3–48 months). There were no differences between the patients with occupational or environmental asbestos exposure (those having a direct contact with contaminated agricultural areas). We did not observe a longer survival time than 4 years (the longest were 48 and 36 months). The other patients did not survive longer than 26 months. There were no age or gender-related differences in the survival time.

4 Discussion

There is many a cause of shoulder ring pain. The pain may arise due to congenital and acquired orthopedic disorders, but is also a sequela of neural diseases or damages, vascular diseases, and of other internal causes. When examining a 'painful shoulder' from the orthopedic standpoint, the most frequent causes taken into consideration are the following: bone fractures or luxations, strains or ruptures of tendons or joint capsule structures, degenerative or inflammatory changes, tumors, scalene muscle attachment anomalies, cervical rib pathologies, scoliosis, thorax deformations, brachial plexus anomalies, and brachial artery pathologies. Other pathologies that can cause shoulder joint pain are rarer and thus taken into account much less frequently in orthopedic anamnesis and physical examination. However, the literature shows that other disorders, particularly originating in the thorax, may lead to the shoulder ring pain. These include lung and pleura anomalies, congenital and acquired diaphragm defects, pathologies of the heart and pericardium, and of other mediastinal structures pathologies like esophagus (Ramponi 2011; Adamietz et al. 2008; Caravati et al. 2001). The present review of mesothelioma cases points attention to those relatively infrequent, non-orthopedic reasons of shoulder ring pain, which may be spuriously attributed to an orthopedic pathology. An interdisciplinary approach and unceasingly diligent diagnostic pursuit are thus sometimes required to resolve the diagnostic uncertainties surrounding the underlying cause of the shoulder ring pain. There are additional non-orthopedic symptoms that may increase the awareness toward a malignant underlying reason of the shoulder pain. Some of the most common and non-specific pleural mesothelioma symptoms are dyspnea (90 % of patients), chest pain connected with chest wall or intercostal nerves infiltration, and cough (Neumann et al. 2013). The present study, in general, confirms those findings, although chest pain, in particular, may be misleading as it is encountered in a wide spectrum of cardiac, pneumological, and orthopedic conditions. Concerning the orthopedic conditions, chest pain is a feature of the inflammation of the sternoclavicular joint or rib cartilage, and of cervical discopathies.

In the present study, the primary localization of mesothelioma was the parietal pleura, which lines the inner surface of the chest wall. The metameric innervation comes from the intercostal nerves. There is anastomosing innervation between the parietal pleura and other chest wall layers, which enables the transmission of pain along the dorsal thoracic nerve and the dorsal scapular to the shoulder area. It is therefore reasonable that the first symptom of pleural mesothelioma can be the shoulder pain, radiating to the neck and scapula as we found in the present study. The patients could not precisely localize the focus of pain; it was diffuse, with radiation to the chest. In some instances, pain radiated the other way around, from the chest to the shoulder area; the direction could be interchangable. The pain intensified with inspiration. These complaints were usually vexing and worrisome enough for the patient to seek orthopedician's advice. Mesothelioma remains a relatively uncommon malignancy, particularly taking into account more widely used counter measures against exposure to asbestos. Nonetheless, it remains a difficult to diagnose, deadly