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MULTIDISCIPLINARY TREATMENT OF MALIGNANT PLEURAL AND PERITONEAL MESOTHELIOMA IN KLAIPEDA UNIVERSITY HOSPITAL. CASE REPORT

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Key words: mesothelioma, asbestos, chemotherapy, HYPEC (hypertermic intra-peritoneal chemotherapy), cytoreductive surgery, DMPM (Differentiated Malignant Peritoneal Mesothelioma), multidisciplinary team, PCI (peritoneal carcinosis index).

Summary

Malignant mesothelioma is an aggressive tumor of serosal surfaces, such as the pleura, the peritoneum, the pericardium and the tunica vaginalis. There is a substantial interest in this disease by part of medical community and the general public because millions of people have been exposed to asbestos fibers, and many articles about the dangers of asbestos had appeared in the press. 80 percent of patients with pleural malignant mesothelioma are male, commonly present with a pleural effusion, associated with breathlessness and often accompanied by chest-wall pain (more than 60 percent of patients). The main cause of malignant mesothelioma is exposure to asbestos – the carcinogen associated with malignant mesothelioma. Indeed, malignant mesothelioma was rare before the widespread use of asbestos, and increasing incidence worldwide is expected to peak in 5 to 10 years.

The pathologic diagnostic of malignant mesothelioma is very difficult even with pathology experts in mesothelioma. Accurate and rapid diagnosis of malignant mesothelioma is important for therapeutic reasons. The most frequent diagnostic problem is the differentiation of malignant mesothelioma and adenocarcinoma – a distinction that is particularly difficult to make when the tumor has invaded the pleura. For many years surgery has proved to be most useful for palliation – for example, for local control of recurrent effusions. Debulking surgery is used in some centers until now. Systemic chemotherapy, cytoreductive surgery, HYPEC and multidisciplinary team discussion can help to cure or extend survival of patients. The case report showed successful multidisciplinary approach treatment for young man with malignant pleural and peritoneal mesothelioma.

Introduction

Malignant mesothelioma is an aggressive tumor of serosal surfaces, such as the pleura and the peritoneum. This tumor type was once rare, but its incidence is increasing worldwide, probably as a result of widespread exposure to asbestos, a factor with which it is associated [1]. There is substantial interest in this disease by part of the medical community and the general public, because millions of people have been exposed to asbestos fibers, and many articles about the dangers of asbestos have appeared in the press. 80 percent of patients with pleural malignant mesothelioma are male, and patients commonly present with a pleural effusion associated with breathlessness and often accompanied by chest-wall pain (more than 60 percent of patients). The combination of an unexplained pleural effusion and pleural pain should raise the suspicion of malignant mesothelioma, even if the initial cytological findings are negative. Weight loss and fatigue are common later in the progression of pleural mesothelioma but are less so at presentation (occurring for less than 30 percent of patients). Although a cytological diagnosis can be made quickly, malignant mesothelioma is usually not diagnosed until two or three months after the onset of symptoms; delays of this length are especially frequent in centers in which the disease is uncommon. Mesothelioma is occasionally discovered incidentally on routine chest radiography. The most common presenting features in patients with peritoneal malignant mesothelioma are distention due to ascites, abdominal pain, and occasionally organ impairment, such as bowel obstruction. In addition to the pleura and the peritoneum, mesotheliomas can occur on other serosal surfaces, such as the pericardium and the tunica vaginalis.

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Because malignant mesothelioma develops covertly within the body cavities, patients usually have fairly extensive tumor involvement by the time they seek care. However, metastases are rarely the cause of death. Local invasion, which is common, causes enlargement of the lymph nodes and may result in obstruction of the superior vena cava, cardiac tamponade, subcutaneous extensions, and spinal cord compression. Miliary spread of malignant mesothelioma can also occur. The contralateral lung or the peritoneal cavity is invaded by pleural mesothelioma in 10 to 20 percent of cases. The most common physical signs of malignant mesothelioma in the chest are related to the underlying effusion (pleural effusion or ascites). Clubbing occurs in less than 1 percent of cases. When pleural mesothelioma progresses, the affected site becomes fixed and cannot expand. Such chest-wall fixation can lead to pneumonia. The physical signs in patients with peritoneal mesothelioma are typically distention and ascites. Subcutaneous masses are almost always associated with prior medical intervention and occur in thoracotomy wounds and previous drainage sites [1,2].

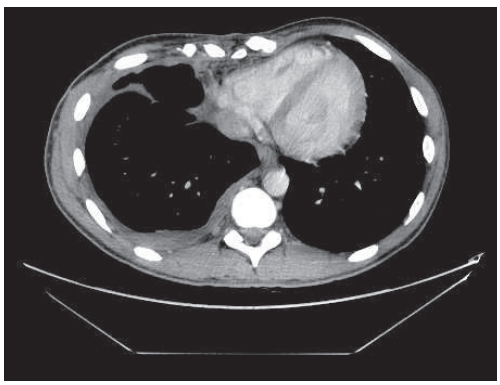
Causes. Asbestos is the principal carcinogen associated with malignant mesothelioma. Indeed, malignant mesothelioma was rare before the widespread use of asbestos. In 1960, the first convincing evidence of a link between malignant mesothelioma and both occupational and incidental asbestos exposure was reported, on the basis of data from South Africa [1]. There are two principal forms of asbestos: long, thin fibers known as amphiboles, one type of which is called blue asbestos, and feathery fibers known as aschrysotile (or white asbestos). It is still debated whether malignant mesothelioma is caused only by amphibole fibers, or if as well by chrysotile fiber. The association of chrysotile with malignant mesothelioma was once thought to be due to contamination of chrysotile with the amphibole tremolite; however, current evidence, particularly from electron microscopical studies, supports the view that chrysotile itself can cause malignant mesothelioma, although at rates lower than those of mesothelioma caused by amphiboles. Malignant mesotheliomas occur initially on the parietal surface of the pleural mesothelium, rather than on the visceral surface. Several mechanisms might account for this finding; one possibility is that the asbestos fibers stick out from the lung surface and cause repeated cycles of scratching, damage, inflammation, and repair in the adjacent parietal mesothelial-cell layer. The increasing incidence worldwide is expected to peak in 5 to 10 years [3-6, 16].

Diagnosis. Accurate and rapid diagnosis of malignant mesothelioma is important for therapeutic and medicolegal reasons. The most frequent diagnostic problem is the differentiation of malignant mesothelioma from adenocarcinoma — a distinction that is particularly difficult to make when the tumor has invaded the pleura. Radiological technic can help when malignant mesothelioma is suspected. Imaging tests are the first step in diagnosing mesothelioma. These tests show the presence of abnormalities. This helps to know where the tumor is and how advanced the cancer may be. Each imaging test has its own purpose, which helps specialist make an accurate diagnosis. X-Ray – this test provides a 2D image of the patient and can show tumor and fluid buildup. This test is used for all suspected diagnoses (pleural, peritoneal, pericardial). Computed Tomography Scan – CT scans are 3D imaging tests that provide more detailed images of anomalies found by X-rays. This is primarily used to diagnose pleural mesothelioma. Positron Emission Tomography Scan – PET scans show the presence of metastasis in the whole body. PET CT can help to choose aggressiveness of treatment strategy. This test is useful in staging. Magnetic Resonance Imaging Scan – MRIs create detailed images of tissue. This test can be used to determine the extent of damage to soft tissue surrounding a tumor. This is also useful to determine if surgery is possible [14, 15, 21, 22].

Cytologic analysis. Cytologic evidence of malignant mesothelioma in the pleural or ascitic fluid is found in 33 to 84 percent of cases. For some patients, sampling by fine-needle aspiration of the tumor is required to make a diagnosis of malignant mesothelioma, particularly when there is no effusion. A group of immunohistochemical markers is important in the differential diagnosis of malignant mesothelioma. As the first step, a marker such as calretinin or the Wilms' tumor 1 antigen (WT1) is used to determine whether the tissue is mesothelial. The second step is to use a marker such as epithelial membrane antigen (EMA; also known as CA15-3 and mucin-1) to determine whether the tissue is malignant. Staining for EMA in a thick peripheral distribution is highly suggestive of malignant mesothelioma. Of the two anti-EMA antibodies, E29 has significantly greater specificity than MC-5. In experienced hands, cytological analysis is sufficient to make a diagnosis with a high level of confidence in approximately 80 percent of cases of malignant mesothelioma [16,19, 20].

Hystopathology. Because cytological findings may be inconclusive or pleural or ascitic fluid may be absent altogether, tumor biopsy is often needed. Closed biopsy (e.g., with the use of an Abrams' needle) is less likely than direct thoracoscopic biopsy to yield positive results. Immunohistochemical staining to show, for example, expression of epithelial membrane antigen on the luminal aspects of the tumor is essential in the diagnostic process. Cytokeratin

staining helps to confirm invasion and to distinguish malignant mesothelioma from sarcoma and melanoma. Malignant mesothelioma is distinguished from adenocarcinoma by the use of specific antibodies. Malignant mesothelioma is characterized by the presence of staining for EMA, calretinin, WT1, cytokeratin 5/6, HBME-1 (an anti–mesothelial cell antibody), or mesothelin (more than 85 percent of epithelioid malignant mesotheliomas are positive for mesothelin) and the absence of staining for antigens such as carcinoembryonic antigen; thyroid transcription factor-1; the tumor glycoproteins B72.3, MOC-31, and Ber-EP4; and the epithelial glycoprotein BG8. Furthermore, other tumors can stain positive with these antibodies (e.g., ovarian carcinoma stains for mesothelin and WT1). Electron microscopy is a useful additional method by which to distinguish malignant mesothelioma from adenocarcinoma or to distinguish desmoplastic or sarcomatoid mesothelioma from fibrous pleuritis. Mesothelioma in situ (atypical



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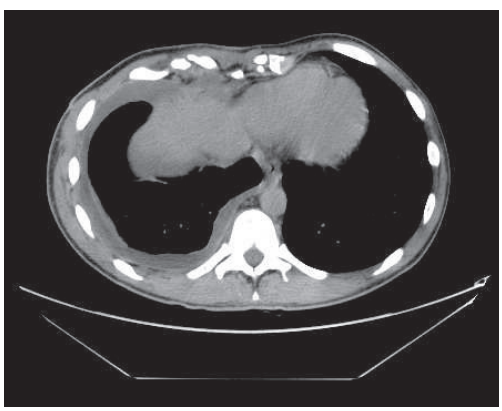

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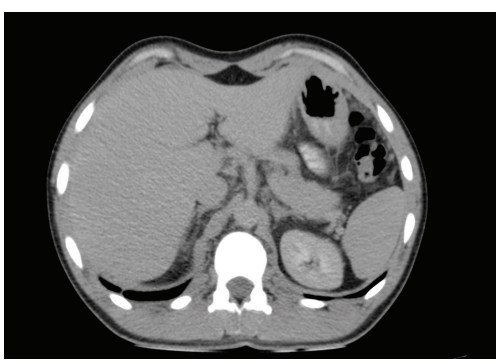

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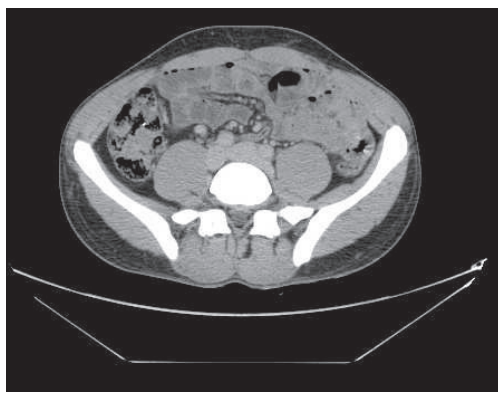

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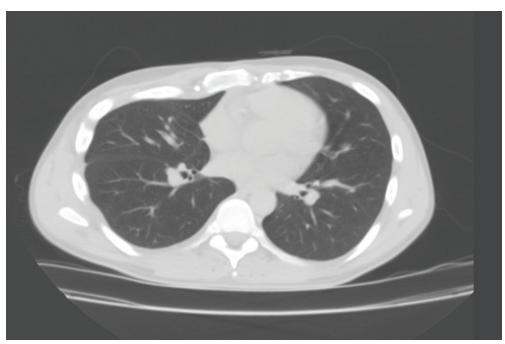

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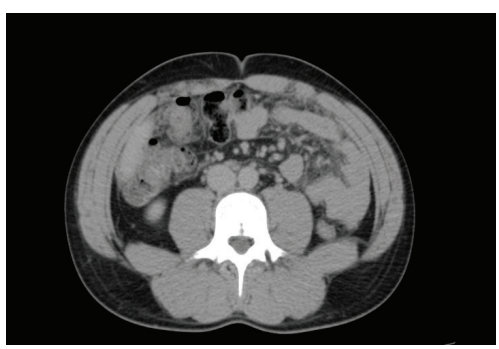


Pic. 6.

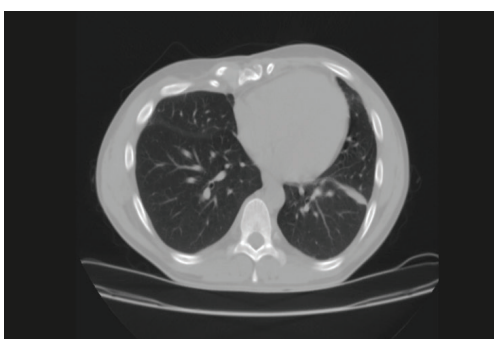
mesothelial proliferation) is hypothesized to be the earliest lesion, akin to cervical dysplastic lesions [7-12, 18].

Treatment. The median survival of patients with malignant mesothelioma from the time of diagnosis is 12 months. Many years surgery has proved most useful for palliation — for example, for local control of recurrent effusions. Debulking surgery is used in main centers [23-27].

Chemotherapy. Until recently, all reviews of chemotherapy for malignant mesothelioma reported poor response rates (typically less than 15 to 20 percent) and, because of these low rates, was not recommended as a standard care [26, 27, 28, 29, 30]. However, a number of multicenter studies are now under way, and several new therapeutic regimens appear to be useful. Pemetrexed is a potent inhibitor of a number of proteins, including thymidylate synthase and dihydrofolate reductase, both of which are required for DNA synthesis. In a multicenter phase 3 study involving 448 patients, those treated with pemetrexed plus cisplatin had a longer overall median survival (12.1 months) than those treated with cisplatin alone (9.3 months) and had an objective response rate (shrinkage of the tumor by at least 50 percent) of 41 percent. Treatment with gemcitabine, a "false nucleotide" that is incorporated into DNA, plus cisplatin resulted in objective response rates of 48 percent and 33 percent in two studies, as well as symptomatic improvement and quality of life benefits.

Radiotherapy. Malignant mesothelioma is resistant to traditional radiotherapy. Local radiotherapy directed to surgical sites prevents seeding of tumor, and radiotherapy can provide palliative relief of somatic chest-wall pain.

Recently, diagnostic and therapeutic aspects of the disease have been re-evaluated as encouraging reports from several centers worldwide on a combined systemic chemotherapy and locoregional treatment approach that uses cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have emerged [31-33]. This new treatment strategy has shown favorable prognosis and has achieved a median survival of up to 60 months and a 5-year survival of 50 percent in selected patients. In the past, no uniform treatments were suggested for patients with DMPM, and survival was largely dependent on the histopathologic subtype of the disease. Several studies have reported reduced survival outcome associated with biphasic or sarcomatoid subtype compared with outcomes associated with the epithelial subtype. A lack of prognostic indicators for optimal patient selection is not surprising. As the disease is rare, most centers have insufficient number of patients, and the treatments employed in these patients have varied greatly. Most studies in the current literature have relatively small samples; therefore, the clinical implications of these reports are limited. Published article [34] which represents a registry of the largest collaborative effort to demonstrate clinical outcomes of patients with peritoneal mesothelioma who were treated by a combined strategy. This allows a more thorough and precise analysis of clinicopathologic and treatment related prognostic parameters. Women have a better prognosis than men. Direct exposure to asbestos was apparent in men, but it was less apparent in women. It is possible that this difference in causation is at least partially responsible for the difference in survival between men and women.



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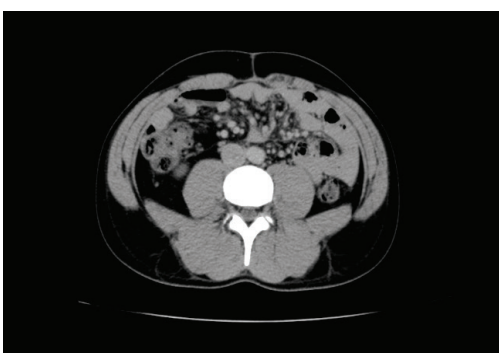

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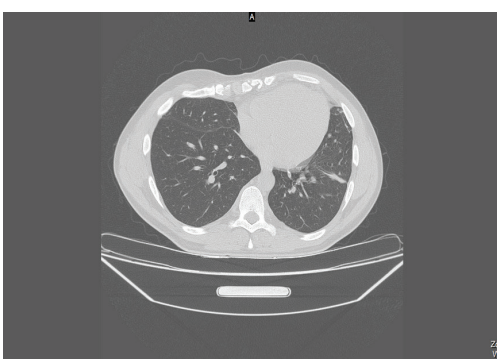

Pic. 9.

Acherman et al reported that women seldom presented with weight loss; a lack of this important poor prognostic symptom suggested less advanced disease. Also, women often sought medical attention with gynecologic complaints caused by DMPM. Diagnoses as a result of nonspecific gynecologic symptoms may have resulted in earlier interventions. A recent study showed that women had more favorable histopathologic features, which might contribute to their better survival.

The sex difference in survival was significant in the univariate analysis, but not in the multivariate analysis, in this study.

Lymph node metastasis is uncommon in patients with DMPM but it is associated with extremely poor prognosis. In this registry, 25 patients had positive lymph nodes identified during surgical exploration; the median survival of these patients was 20 months versus 56 months for patients without positive lymph nodes. Yan et al [33] reported that seven patients had positive lymph nodes. The median survival of these patients was 6 months, and the 1-year and 2-year survival rates were 43 percent and 0 percent respectively. Ninety-three patients had absence of lymph node involvement; the median survival of these patients was 59 months, and 5- and 7-year survival rates were 50 percent and 43 percent, respectively. The crucial importance of lymph node metastasis should encourage surgeons to vigorously search for abnormal nodes when they perform CRS. Any enlarged or firm lymph nodes should be submitted for pathologic evaluation separately from the rest of the specimens. It should become current surgical practice to sample all suspicious lymph nodes in patients with DMPM to better determine prognosis and to provide more knowledge in the management of these patients. Nearly all peritonectomy centers agree that multidisciplinary approach, systemic chemotherapy, adequate cytoreduction, HYPEC are one of the most significant prognostic factors for long-term survival [31-34]. Adequate cytoreduction is related to the pretreatment tumor load and the surgeon's technical ability to eradicate gross disease. Unlike pseudomyxoma peritonei, DMPM generally does not spare the peritoneal surfaces of the small intestine, which limits the ability to achieve CC. Clear resection margins are difficult to obtain.

The recognition that surgery alone may not provide adequate local disease control has provided the rationale for combining CRS with HIPEC. CRS aims to remove all peritoneal tumors together with complete lysis of adhesions between the bowel loops, which would create an optimal situation for adjuvant intraperitoneal chemotherapy.

Chemotherapy is administered intraoperatively to allow direct chemotherapy and tumor-cell contact and to minimize systemic toxicity. [31-34]. Hyperthermia has had direct cytotoxic effects in both temperature and time-dependent manners. Heat increases the depth of penetration of chemotherapy [31] and synergizes the cytotoxic drugs selected for intraperitoneal use at the time of surgery [33]. Although CRS combined with HIPEC has showed promising results, a prospective comparison of HIPEC versus no HIPEC is not available. Also, no definitive information concerning optimal choice of chemotherapy agents in HIPEC exists. The difficulties of performing such trials in a rare disease like DMPM should be acknowledged. Minimum data was set for all patients undergoing the combined treatment between 1989 and 2009. The standardized, quantitative, prognostic indicators, such as CC score and PCI, were published in 1996. The main limitation of this study is that the data were nonrandomized; thus, unknown confounders that could influence outcome may exist. It is possible that the improved survival in this study compared with historical controls reflected a lead-time bias, in which patients underwent surgery earlier in their natural courses of disease. This could be related to modern diagnostic technologies and increased awareness of surgical treatment options, which would prompt referral to appropriate centers. Nevertheless, the results of this study should encourage early diagnosis and active treatment of DMPM. Although multivariate analysis has identified four prognostic factors that might have contributed to the improved survival results, the true significance of each factor is difficult to assess when in terrelated factors are entered into the analysis. One must bear in mind the limitation of this methodology when interpreting the results. To prove the relevance of HIPEC, additional evaluation in a prospective manner is required. The main value of this experience is to provide a benchmark against which the results of future clinical trials will be judged. Meanwhile, in the absence of level-1 clinical evidence, those entrusted with the care of patients with peritoneal mesothelioma inevitably will be challenged with difficult decisions to share with their patients as together they seek balance between risk and benefit.

Peritoneal mesothelioma is disease, which previously was considered a preterminal condition, now can be treated with CRS and HIPEC at experienced centers to provide a benefit in terms of long-term survival. With a greater proportion of patients undergoing a well-defined treatment plan, more in-depth knowledge can be gained in the diagnosis, radiology, and histopathology of this rare disease. The roles of novel systemic chemotherapy and targeted treatments in patients with DMPM remain to be evaluated, and integration into the combined therapy has yet to be determined [30].

The aims of this study: to describe very rare case pe-

ritoneal/ pleural malignant mesotheliomas and successful multidisciplinary treatment with long survival.

Case report

A 28 years old man presented with a cough, dyspnea, fatigue and tiring. He smokes 20 cigarettes per day. Patient has a congenital chest deformity. He had no history of tuberculosis in the childhood. He was not exposed to asbestos in his work. Due symptoms, patient was tested in October 2014, and the X-ray showed a shadow in the right chest caused by the presence of fluid in the pleural cavity. Ultrasound demonstrated ascites in the abdomen and a mass of 15 mm above left clavicle lymph node. CT scans were performed [Picture No.1, 2, 3].

The diagnosis of pleural and peritoneal mesothelioma, epithelioid type was confirmed after laparoscopy and VATS pleural resection in November 2014. Due disseminated pleural and peritoneal mesothelioma patient started palliative treatment. Patient was indicated to receive palliative chemotherapy only. Chemotherapy with cisplatin 75 mg/m2 and pemetrexed 50 mg/m2 was started and continued for 6 courses. After the treatment 3 courses was confirmed minor partial response and after 6 courses CT scans showed and confirmed major partial remission in peritoneal and full remission in pleural cavities [Picture No. 4, 5, 6].

Multidisciplinary team concluded to perform random pleural cavity biopsies for confirmation complete response in April 2015. Pleural fibrosis and no neoplastic cells were detected morphologically. Diagnostic laparoscopy procedure was performed and confirmed morphologically peritoneal epithelioid mesothelioma with PCI – 12 (peritoneal carcinosis index).

In May 2015 patient was performed CCR (complete cytoreductive surgery) and HYPEC (hyperthermic intraperitoneal chemotherapy) 42°C concurrently with cisplatin 75 mg/m2 for 1 hour exposition. There were no surgery complications or with intraperitoneal chemotherapy associated adverse events. Patient was discharged from the hospital after 11 days in very good condition, ECOG 1. Histopathology investigation after surgery showed epithelioid mesothelioma in peritoneal, diaphragm and colon surfaces. Radical citoreductuve surgery was performed.

Follow- up after 22 months: patient has no evidence of progression since the diagnosis [Picture No. 9]. Currently patient is working. ECOG- 0, complete remission can be seen on CT and MRI in recent by RECIST 1.1.

Conclusion

Malignant pleural and peritoneal mesothelioma which previously was considered a preterminal condition, now can be treated with CRS and HIPEC at experienced centers to provide a benefit in terms of long-term survival and rare cases can be cured. With a greater proportion of patients undergoing a well-defined treatment plan, more in-depth knowledge can be gained in the diagnosis, radiology and histopathology of this rare disease.

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PLEUROS IR PILVAPLĖVĖS PIKTYBINĖS MEZOTELIOMOS GYDYMAS, DALYVAUJANT KLAIPĖDOS UNIVERSITETINĖS LIGONINĖS MULTIDISCIPLININEI KOMANDAI. KLINIKINIS ATVEJIS

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Raktažodžiai: mezotelioma, asbestas, chemoterapija, HYPEC (hyperterminė intraperitonealinė chemoterapija),

citoredukcinė operacija, DPPM (diferencijuota piktybinė peritonealinė mezotelioma), multidisciplininė komanda, PKI (peritoninės karcinomatozės indeksas).

Santrauka

Pilvaplėvės ir pleuros piktybinė mezotelioma priskiriama prie labai agresyvių serozinių kūno dangalų navikų. Dažniausiai pažeidžiama pleura, pilvaplėvė, perikardas ir retais atvejais vaginalinis dangalas. Pagrindinė priežastis, kuri sukelia šią sunkią navikinę ligą, yra asbesto skaidulų patekimas per kvėpavimo takus į plaučius. Sergamumas šia liga nuolat auga ir sergamumo pikas, manoma, kad pasieks po 5-10 metų. Gydymui buvo atliekamos labai agresyvios citoredukcinės operacijos, skiriama chemoterapija, tačiau pacientų išgyvenamumas buvo labai trumpas. Su naujųjų technologijų atėjimu ir mokslui labiau gilinantis į mezoteliomos progresavimo kelius, atsivėria vis didesnės galimybės šiuos pacientus ne tik gydyti, bet ir išgydyti. Multidisciplininės komandos darbas suteikia viltį pacientui pasveikti. Taikomos pleuros ir pilvaplėvės citoredukcinės operacijos, panaudojanat hiperterminę intraperitonalinę chemoterapiją. Šiame straipsnyje pateikiamas sėkmingas klinikinis piktybinės pleuros ir pilvaplėvės mezoteliomos gydymo atvejis, kai jame dalyvavo Klaipėdos universitetinės ligoninės multidisciplininė komanda.

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