Malignant peritoneal mesothelioma: a multicenter study on 81 cases

V. de Pangher Manzini¹, L. Recchia¹, M. Cafferata², C. Porta³, S. Siena⁴, L. Giannetta⁴, F. Morelli⁵, F. Oniga⁶, A. Bearz⁷, V. Torni³ & M. Cinquini⁸

¹Division of Medical Oncology, Department of Internal Medicine and Oncology, Montefalco Hospital, Montefalco; ²Division of Medical Oncology, Department of Internal Medicine and Oncology, Casale Monferrato Hospital, Casale Monferrato; ³Department of Medical Oncology, Istituto di Ricerca e Cura a Carattere Scientifico, San Matteo University Hospital Foundation, Pavia; ⁴The Falck Division of Medical Oncology, Niguarda Ca’ Granda Hospital, Milan; ⁵Department of Oncology, Istituto di Ricerca e Cura a Carattere Scientifico, Casa Sollievo della Sofferenza, San Giovanni Rotondo; ⁶Division of Medical Oncology, Department of Oncology, Venice-Mestre Hospital; ⁷Department of Medical Oncology, Centro di Riferimento Oncologico - Istituto di Ricerca e Cura a Carattere Scientifico, Aviano and ⁸Department of Oncology, Mario Negri Institute, Milan, Italy

Background: Malignant peritoneal mesothelioma (MPM) is a rare disease characterized by a difficult diagnosis, different types of presentation, variable course and poor prognosis.

Materials and methods: Eighty-one patients with MPM observed in 14 Italian oncology institutions from 1982 to 2007 have been examined with the aim of delineating the history of MPM.

Results: Presentation symptoms were ascites, abdominal pain, asthenia, weight loss, anorexia, abdominal mass, fever, diarrhea and vomiting in various associations. Computed tomography scan and echotomography signs were ascites, abdominal mass and peritoneal thickening. Peritoneal fluid cytology (61 cases) was positive for mesothelioma in 31 and for malignancy, not mesothelioma, in 13. Laparoscopy was carried out in 40 cases and laparotomy in 36. Thrombocytosis was present in 59 cases. Associated tumors diagnosed during the lifetime were colorectal cancer in two cases and cheek carcinoma, thyroid carcinoma, tongue carcinoma, bladder carcinoma and testicular seminoma. Thirty patients were treated with surgery and 45 with chemotherapy. The median survival time from diagnosis is 13 months. Ascites, fever and vomiting were signifcative variables at presentation; only vomiting holds significance in a multivariate analysis.

Conclusions: MPM is a disease with various types of presentation, frequently associated with thrombocytosis, sometimes with other tumors. Survival and diagnosis time can differ in various types of MPM. Prognosis is poor.

Key words: asbestos, diagnosis, mesothelioma, peritoneum, prognosis, thrombocytosis

introduction

Mesothelioma is a neoplasm of the serosal surfaces. It may involve the pleura, less frequently the peritoneum and in a small percentage of cases the pericardium or the tunica vaginalis testis. Malignant peritoneal mesothelioma (MPM) with an incidence of ~250 new cases per year in the United States is a very rare type of cancer [1]. A causal relationship with asbestos exposure is widely accepted [2], but an association with exposure to other mineral fibers, chronic peritonitis, remote abdominal radiation and simian virus 40 was also indicated to play a role in the pathogenesis of this disease [3, 4]. Owing to the rarity of the disease, only few papers on MPM report a consistent number of cases: most of them report small series and single cases, sometimes with an unusual clinical presentation or course. Diagnosis of MPM can be difficult, so incidence and mortality are probably underestimated [5]. Radiological assessment is usually carried out with computed tomography (CT) scan and echotomography (ECT), but more recently magnetic resonance imaging, positron emission tomography (PET) and CT/PET have also been utilized. The histology of an adequate specimen and cytology are very important for diagnosis. Therapy includes surgical and medical treatment, each of these alone or in combination. Prognosis of MPM is poor, with a median survival <1 year [6], although in recent years new therapeutic strategies, like combined approach with cytoreductive surgery and perioperative i.p. chemotherapy, have been proved to be able to considerably improve the survival in selected cases [7]. Prognostic factors such as age, pain, ascites, fever, weight loss, performance status (PS), tumor size, histological type, completeness of cytoreduction and biologic markers have been investigated [3, 6, 8]. Female patients have been reported to have an improved survival outcome for reasons that are not understood [9]. Recently, a study on 15 patients observed at the Montefalco Hospital showed a variability of the clinical presentation in MPM with some not well-known pictures. The author indicated a new clinical classification of MPM based on the clinical presentation into three clinical types (classic, medical and surgical) characterized by different clinical courses [10]. The present study reports 81 cases of MPM observed at 14 Italian oncology institutions with the aim of delineating the history of MPM.
materials and methods

We carried out a retrospective cohort study on patients with MPM observed in 14 Italian oncology institutions from 1982 to 2007. To be eligible, patients were required to have a cytology- or histology-proven diagnosis of MPM. For every patient, 69 items regarding the whole course of disease were collected, such as demographic data, asbestos exposure, clinical presentation, PS (according to Eastern Cooperative Oncology Group scale), diagnostic work-up (CT scan, ECT, peritoneal fluid cytology, histology and surgical investigations like laparoscopy and laparotomy), thrombocytosis (in different phases of the disease: at presentation, after 3 months and in the advanced phase), clinical course, treatment, concomitant diseases, causes of death and necropsy data. Thrombocytosis was defined with a platelet count >400 000/mm3 and anemia with a hemoglobin value <12 g/dl in men and 11 g/dl in women. According to the previous paper, the clinical presentation was classified into three types: the classic one with abdominal pain, ascites and abdominal mass; the medical one with abdominal pain, weight loss, fever, diarrhea, vomiting, anemia, anorexia, erythrocyte sedimentation rate >225, anemia and thrombocytosis; and the surgical one with hernia, ileus and abdominal perforation. Median survival time, in the whole group and according to the type of clinical presentation, was computed from the time of diagnosis. Moreover, diagnosis time (from first symptoms to diagnosis) was computed. Actuarial survival curves were generated using the method of Kaplan and Meier (Kaplan and Meier, 1958). To allow for statistical adjustments for prognostic variables (i.e. abdominal pain, ascites, abdominal mass, weight loss, fever, diarrhea, vomiting, anemia, anorexia, anemia and thrombocytosis), a Cox proportional hazards model was used, and hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs) were calculated. All probability values were two sided and a level of $P < 0.05$ was considered as statistically significant.

Statistical analysis was carried out with the version 9.1 of the statistical software SAS (SAS Institute, Inc., Cary, NC).

results

Fourteen institutions recruited 81 patients in this study from 1982 to 2007: 57 men and 24 women (mean age 64 years, 19–85: 63 for men and 68 for women). The history of asbestos exposure was positive in 42 cases (34 men) and doubtful in nine (eight men).

presentation

Symptoms at the clinical presentation in the whole series and for the presentation type are listed in Table 1. Combining the presentation symptoms into the three groups (classic, medical and surgical), presentation was classified as classic in 59 cases on 81 (73%), surgical in 13 on 81 (16%) and medical in 9 on 81 (11%).

diagnosis

CT scan was carried out in 71 patients and ECT in 43. Table 2 reports CT scan and ECT remarks in the various types of clinical presentation. Peritoneal fluid cytology, carried out in 61 cases, was positive for mesothelioma in 31; positive for malignancy, not mesothelioma, in 13; negative with associated atypical or activated mesothelial cells in nine and negative in eight. The main diagnostic procedures were laparoscopy in 40 cases (49%) and laparotomy in 36 (44%), both with a very high diagnostic performance. Therefore, diagnosis has been surgical in most cases with a wide exploration of abdomen and adequate surgical specimens. As regards the blood cell count, thrombocytosis was present in the different phases of the disease, in 59 cases on 81 (73%), exactly the same rate of anemia evaluated only at the clinical presentation (59 on 81). PS (60 cases assessable) was zero in 12 (20%), one in 27 (45%), two in 16 (27%) and three in five (8%).

therapy

Thirty patients were treated with surgery. There were only seven with peritonectomy and concomitant i.p. hyperthermic chemotherapy, the others with minor surgery. Forty-five patients were treated with chemotherapy; most common regimens were pemetrexed and cis/carboplatin in 10 patients and gemcitabine and cis/carboplatin in 11. Twenty-one patients were treated with surgery combined with systemic chemotherapy.

associated diseases and outcome

Associated non-neoplastic diseases are listed in Table 3. In seven patients, a diagnosis of another malignant neoplasia during lifetime was made. Associated tumors were colorectal cancer in two cases and cheek basocellular carcinoma, papillary thyroid carcinoma, tongue carcinoma, bladder carcinoma, testicular seminoma, lung non-small-cell carcinoma and ileus neuroendocrine carcinoma in one case each. Tongue and lung carcinoma were diagnosed at different times in the same patient, like seminoma and neuroendocrine carcinoma in another patient. All these patients were treated with surgery;

Table 1. Presentation symptoms in the whole series and for presentation type

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Classic presentation</th>
<th>Medical presentation</th>
<th>Surgical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>n</td>
<td>%</td>
<td>Patients</td>
</tr>
<tr>
<td>Ascites</td>
<td>62</td>
<td>81</td>
<td>77</td>
<td>51</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>56</td>
<td>81</td>
<td>69</td>
<td>38</td>
</tr>
<tr>
<td>Anemia</td>
<td>35</td>
<td>81</td>
<td>43</td>
<td>24</td>
</tr>
<tr>
<td>Weight loss</td>
<td>26</td>
<td>81</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>Anorexia</td>
<td>24</td>
<td>81</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>24</td>
<td>81</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Fever</td>
<td>18</td>
<td>81</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
<td>81</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>81</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>
Table 2. CT scan and echotomography and types of clinical presentation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Total patients</th>
<th>%</th>
<th>Patients</th>
<th>Total</th>
<th>%</th>
<th>Patients</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT ascites</td>
<td>47</td>
<td>59</td>
<td>80</td>
<td>5</td>
<td>13</td>
<td>56</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>CT abdominal mass</td>
<td>19</td>
<td>59</td>
<td>32</td>
<td>5</td>
<td>13</td>
<td>56</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>CT peritoneal thickening</td>
<td>37</td>
<td>59</td>
<td>63</td>
<td>6</td>
<td>13</td>
<td>67</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>CT mesenterial thickening</td>
<td>17</td>
<td>59</td>
<td>29</td>
<td>2</td>
<td>13</td>
<td>22</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>ECT ascites</td>
<td>32</td>
<td>59</td>
<td>54</td>
<td>3</td>
<td>13</td>
<td>33</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>ECT abdominal mass</td>
<td>11</td>
<td>59</td>
<td>19</td>
<td>2</td>
<td>13</td>
<td>22</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>ECT peritoneal thickening</td>
<td>5</td>
<td>59</td>
<td>8</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

CT, computed tomography; ECT, echotomography.

Table 3. Associated non-neoplastic diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Total patients</th>
<th>%</th>
<th>Patients</th>
<th>Total</th>
<th>%</th>
<th>Patients</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>30a</td>
<td>81</td>
<td>37</td>
<td>5</td>
<td>13</td>
<td>56</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Respiratory</td>
<td>22b</td>
<td>81</td>
<td>27</td>
<td>3</td>
<td>13</td>
<td>33</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>24c</td>
<td>81</td>
<td>30</td>
<td>2</td>
<td>13</td>
<td>22</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>24d</td>
<td>81</td>
<td>30</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

aGastritis in nine cases, colon diverticulitis in six, duodenal ulcer in six, hiatal hernia in five, esophagitis in two, colon polyposis in two, hepatic cirrhosis in two and gastric ulcer and cholelithiasis in one.
bAsbestos in 15 cases, chronic obstructive pulmonary disease in seven, bronchopneumonia in two and previous tuberculosis in one.
Arterial hypertension in 12 cases, ischemic cardiopathy in six, pulmonary hypertension in three and atrial fibrillation, cardiac failure and thromboembolism in one.
dDiabetes in nine cases, prostate hypertrophy in four, disk hernia in three, varicosity in two and dyslipidosis, gout, goiter, renal insufficiency, nephrolithiasis and poliomyelitis in one case.

Therefore, the diagnosis of the associated neoplasia was made on surgical specimens with a clear differentiation of MPM from peritoneal carcinomatosis. There were two autopsy diagnosis tumors: prostate carcinoma and papillary thyroid carcinoma. The main causes of death, assessable in 41 cases, were cachexia in 29 cases, intestinal obstruction in 14 and pulmonary thromboembolism in five. Figures 1 and 2 report the survival curves from the diagnosis, respectively, in the whole series and in the different types of clinical presentation. The median survival time from the diagnosis in the whole series is 13 months (95% CI 7.5–46): 17 months (10 to upper limit not reached) in classic presentation, 5 months (4–13) in medical and 12 months (2 to upper limit not reached) in surgical. The median diagnosis time (first symptoms to diagnosis) in the whole series is 2 months (0–29) and 2 months (0–30) in the classic presentation, 5 months (0–14) in the medical and 1 month (0–12) in the surgical. The most significant variables associated with death, evaluated at the presentation of MPM, have been ascites, fever and vomiting (Table 4). The variables with a high level of significance ($P < 0.001$) have been analyzed in a multivariate model; only vomiting holds significance (HR 8.18, $P < 0.0001$). Evaluating the same data from the start of the therapy the results are different: in this case, weight loss, fever and abdominal mass are significant in a multivariate analysis (Table 5).

**Discussion**

The large series of this multicentric retrospective study was recruited over a very long period of time (1982–2007). For this reason some of the data, owing to the progress in diagnosis and therapy tools in the past 25 years, are not homogeneous and comparable, particularly for treatment. Nevertheless, the series, collection of data regarding the whole course of the disease, is complete and suitable for a description of the history of MPM. Most cases were derived from two Italian areas with a very high incidence of mesothelioma, Monfalcone and Casale Monferrato. In both areas, mesothelioma is related to occupational asbestos exposure like in shipyards in Monfalcone and the Eternit factory in Casale Monferrato.

Comparing peritoneal with pleural mesothelioma, there are some differences in sex and age: a higher rate of women (29.3%) and a lower mean age (64 years) in MPM (V. de Pangher Manzini, unpublished data). Perhaps, the type and the level of asbestos exposure may play a still unidentified role, but this remains only a hypothesis. Moreover, peritoneal mesothelioma in women shows some peculiar behavior regarding the differential diagnosis with genitourinary neoplasm, the clinical course and the prognosis [11, 12].

The rate of positive exposure to asbestos (59.6% in men and 33.3% in women; Table 3) is lower than expected for a disease strictly related to asbestos, but the long latent period of mesothelioma and the difficulty in identifying remote exposures can explain these data.

Even if the clinical presentation of MPM is characterized in the majority of the cases by the onset of abdominal symptoms due to ascites and/or abdominal mass, there are also some unusual types of presentation. In particular, two authors analyzed the presentation of MPM, connecting it with the clinical course. de Pangher Manzini [10] in a mono-institutional series consisting of 15 cases observed at the Monfalcone hospital classified MPM presentation into three types: the classic (40% of cases), the surgical (33%) and the medical (27%). In his experience, different presentation was also related to a different diagnosis time, longer in the medical type, although a statistical evaluation was not carried out because of the limited number of cases. The paper also reports...
a review of the literature about the topic. Sugarbaker et al. [13] reports a series of 51 cases and distinguishes three types of presenting symptoms, each one with the same frequency: the ‘wet type’ with malignant ascites, the ‘dry-painful’ type with mass causing pain and the ‘combined type’ characterized by both pain and ascites. In addition, Sugarbaker describes a little number of cases presenting like an acute abdomen. The two experiences show both analogies and differences. The wet and the dry-painful types of the Sugarbaker experience are grouped together in the classic type of the de Pangher series. Both series underline the possibility of a surgical presentation of MPM, whereas only de Pangher describes the medical type as a very peculiar form of MPM presentation, reported in the literature only in small number of cases [10]. In the present study, the rate of nonclassic type (surgical in 16% of cases and medical in 11%) has been lower than that in the previous study. On the whole, abdominal pain is the mostly represented symptom in the three different types of presentation, whereas ascites predominates in the classic type and systemic symptoms (fever, weight loss and asthenia) in the medical (Table 1). Moreover, the possibility of an unusual presentation of MPM must be kept in mind in the context of a clinical picture resembling inflammatory bowel disease and in the presence of intestinal obstruction, perforation and incarcerated hernia, particularly when histories of asbestos exposure and ascites are present.
Abdominal mass 6.43 1.54–26.79 6.53 0.0106
Weight loss 0.22 0.05–0.95 4.14 0.0419
Vomiting 8.34 2.94–23.62 15.93 <0.0001
Diarrhea 2.05 0.79–5.35 2.17 0.1404
Fever 2.52 1.15–5.71 4.91 0.0267
Diabetes 2.05 0.79–5.35 2.17 0.1404
Anemia 0.76 0.32–1.82 0.38 0.5356
Abdominal mass 0.93 0.396–2.18 0.03 0.8686
Abdominal pain 1.68 0.66–4.26 1.19 0.2759

Table 5. Variables at the beginning of the therapy

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>χ²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>0.22</td>
<td>0.03–0.95</td>
<td>4.14</td>
<td>0.0419</td>
</tr>
<tr>
<td>Fever</td>
<td>39.17</td>
<td>5.62–273.07</td>
<td>13.70</td>
<td>0.0002</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>6.43</td>
<td>1.34–26.79</td>
<td>6.53</td>
<td>0.0106</td>
</tr>
</tbody>
</table>

Malignant peritoneal mesothelioma; CI, confidence interval.

ECT and CT scan are basilar in the initial evaluation of all patients. CT scan displays more details than ECT particularly for peritoneal thickening; ascites and peritoneal thickening are the most frequent signs in the classic and medical presentations and abdominal mass and peritoneal thickening in the surgical (Table 2).

Table 4. Variables at presentation of MPM associated with death

In this series, the peritoneal fluid cytology, a simple diagnostic test usually carried out in all patients with ascites of unknown origin, with a high rate of positivity (72% for mesothelioma and malignancy altogether) or suspect (15%) provides useful information, like in other experiences [14, 15].

Subsequent investigations included laparoscopy and laparotomy, which deserve a very high diagnostic performance driving to the correct diagnosis in all patients. Today, laparoscopy, for its minor invasiveness, represents the diagnostic tool of choice.

Thrombocytosis in mesothelioma deserves particular interest. It is well known in pleural mesothelioma [16], but in MPM, it presents even higher rates. So, in this series, thrombocytosis was present, in the different phases of the disease, in 12 of 59 cases (73%). We believe that thrombocytosis can represent a strong suspect for MPM in patients with ascites or with other types of presentation.

Anemia has also been frequent (59 cases on 81), but anemia is very common in various neoplastic and non-neoplastic abdominal diseases, therefore it appears to be less distinctive.

The very long observation period of this series (1982–2007) and the progress in diagnosis and treatment of MPM that occurred in the same period make our data unsuitable to draw any conclusions about the therapy for MPM. All that can be recorded is the variable association of different types of therapy in various patients but not in the present manner in which surgery, chemotherapy and hyperthermia are delivered in an integrated approach, the only one that can substantially improve survival in selected patients [17, 18].

The analyses of the diseases associated with MPM are interesting for several reasons: (i) non-neoplastic diseases, particularly those affecting the gastroenteric area, can mask symptoms of MPM with a consequent delay in the diagnosis and (ii) neoplastic diseases for the study of asbestos-associated tumors [2] and for the complexity of therapeutic needs in patients affected by more than one single tumor. There are few reports of associated tumors: a case of coexisting bladder transitional cell carcinoma [19], a case of second tumor in undefined site at autopsy [20], two necropsy cases of prostate and lung carcinoma, respectively [21], and a simultaneous case of rectal carcinoma [22, 23]. In fact, in this experience, MPM appears as a devastating illness leading the patients to cachexia and intestinal obstruction in a terminal phase characterized by a very high need for palliative care. Moreover, all patients with associated tumors died of MPM itself, confirming the poor prognosis of the disease.

The mean survival time from the diagnosis in the whole series is rather high (13 months, range 12–36), comparable with that of other series [12, 24, 25], higher than some old series [26–28] and lower than other recent, selected series [3, 7, 13, 18].

Only few papers analyzed the prognostic factors in MPM. Male gender, age ≥53 years, loss of weight, more extensive tumor volume and sarcomatoid or biphasic histology were negative prognostic factors for Acherman et al. [3]; only age for Antman et al. [5]; sarcomatoid or biphasic histology for Cerruto et al. [29]; completeness of cytoreduction, PS and mitotic count for Deraco et al. [8]; age, tumor biology, lack of invasive tumor growth and minimal residue after tumor resection for Feldman et al. [18] and mesothelioma nuclear size in multivariate analysis for Yan et al. [30]. In our experience, analyzing the symptoms at presentation, only vomiting holds significance in a multivariate model, whereas at the beginning of therapy weight loss, fever and abdominal mass are significative prognostic factors. In the first case, vomiting can be related to the acute abdominal presentation of the surgical type and in the second to the late diagnosis of MPM at an advanced phase of the disease.

In conclusion, in this large multicentric retrospective study, MPM appears as a disease characterized by various types of presentation, each one with different survival times, and by a poor prognosis. Diagnosis can be carried out by ascitic fluid cytology, CT scan and laparoscopy. Very peculiar appears the association with thrombocytosis. Also the association with other neoplastic and non-neoplastic diseases deserves interest. In selected patients, the combination of surgery, chemotherapy and hyperthermia can substantially improve the outcome.

Finally, we would like to stress the importance of an early diagnosis of MPM for an adequate treatment of this poor prognosis disease, but an important question still remains open: how to arrive to an early diagnosis of MPM.

Acknowledgements

The authors thank Stefano Cobelli, Alessandro Bertolini, Fabio Malugani, Gianpiero Fasola, Ornella Belvedere, Carmine Pinto,
Antonella Marino, Domenico Errante, Savina Aversa and Romana Segati for providing data of their patients.

references


