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Case Report

Molecular changes of malignant mesothelioma in the testis and their impact on prognosis: analyses of two cases

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Abstract: Malignant mesothelioma is a rare and aggressive tumour, generally asbestos-related. When the tumour arises in the pleura or peritoneum a non-occupational or environmental asbestos exposure has also been reported. The latency period from the initial asbestos exposure to the clinical diagnosis is variable but usually long, sometimes as long as 30-40 years. Malignant mesothelioma of the tunica vaginalis testis (MMTVT) is extremely rare; in Italy, the standardized incidence rate for MMTVT is 0.2 cases per million inhabitants. Usually, in this site the tumour appears to be idiopathic in nature but exceptionally, an asbestos exposure has been documented. Here, we report two patients with locally advanced disease; an occupational history of asbestos exposure was ascertained in one case. Radical surgery was performed and adjuvant chemotherapy was administered only in one case.

Keywords: Mesothelioma, testis, microarray-comparative hybridization, prognosis

Introduction

Malignant mesothelioma (MM) is a tumor derived from mesothelial cells of the serous cavities, normally asbestos-related and with a poor prognosis. Cases originating from the tunica vaginalis testis account for only 0.3%-5% of all cases of MM [1]. Since the first cases described by Barbera *et al* [2], just over 250 cases of malignant mesothelioma of the tunica vaginalis have been reported [3-10].

Trauma, previous herniorrhaphy and long-standing hydrocele have been considered predisposing factors, whereas asbestos association has been described only in a few cases [3, 11-17]. Clinically, the tumor is difficult to suspect, and the diagnosis is generally late. In fact, patients typically present signs and symptoms that mimic more common inguino-scrotal problems [9].

Hydrocele (>50%) with or without a paratesticular or testicular mass (32%), are the conditions most frequently observed. Preoperative ultrasonographic diagnosis can be difficult due to the small size of the neoplastic nodules and the presence of papillary exophytic lesions without infiltration. Consequently, early diagnosis is most often made on an intraoperative suspicion confirmed after histological examination.

Only advanced mesotheliomas may invade the testis, the skin, spreading into the peritoneum and loco-regional lymph nodes. Retroperitoneal and supra-clavicular lymph nodes may be involved and metastases in liver, lung and bone have been reported [10]. The median survival is 23 months and patients rarely survive much longer [11]. An aggressive clinical course is typical, especially in tumors that have not been completely excised at the outset. In any case, there is no significant evidence that conserva-

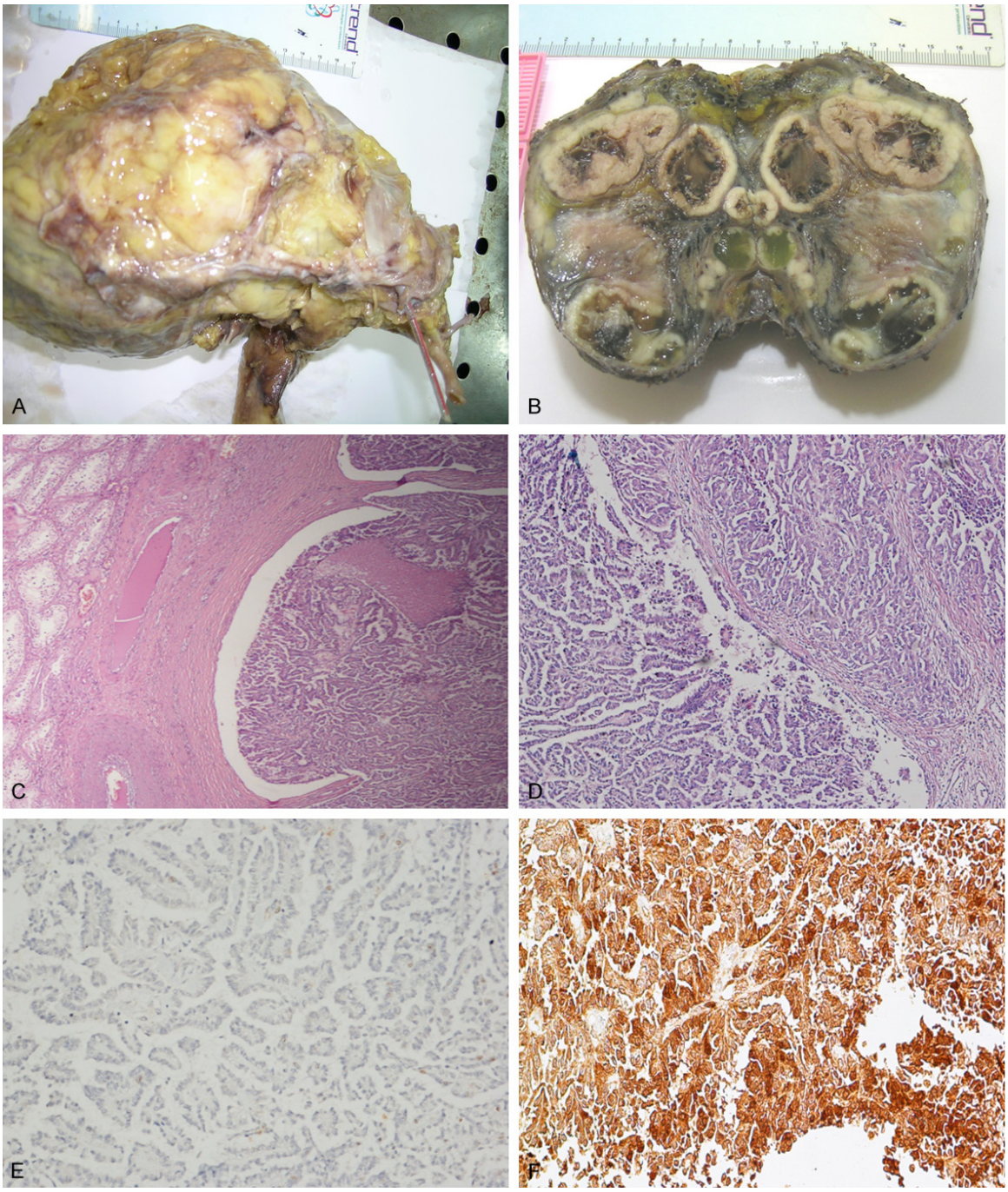


Figure 1. *Case 1*. A. Gross appearance of the left testis; B. The cut surface: the tumor arising from the tunica vaginalis and invading the testicular parenchima. C. Tumor cell had an infiltrative growth pattern (HE, ×100). D. Epithelioid tubulo-papillary pattern (HE, ×200). E. Immunohistochemical staining for WT-1 (negative espression, ×200). F. Calretinin (strong positivity, ×200).

tive or radical surgery influences survival because after radical or palliative treatment the prognosis remains poor and the median survival is less than 23 months [11].

Recently, molecular studies have been performed on MM samples to define genetic characteristics of MM and identify molecular markers which may assist diagnosis and indicate their impact on prognosis and treatment [1]. Little is known about the genetic events that trigger MM and their relation to the poor outcome [18, 19]. Molecular changes consist of an altered expression and activation or inactiva-

tion of critical genes in oncogenesis, especially tumor suppressor genes at 9p21 (INK4) and 22q12 (NF2) loci. Correlation of these molecular alterations with shorter survival or shorter time to relapse has been reported [18, 20]. Other studies correlated the total number of chromosomal alterations with survival. A shorter survival time was correlated to a greater number of genetic alterations [18, 21].

Here we describe the diagnosis and course of two cases of MM localized in the tunica vaginalis, including immunohistochemical analysis and comparative genomic hybridization (CGH) findings.

Cases presentation

Case 1

A 77-year-old man came to hospital in October 2008 with a painless left inguinal swelling that had been present for about 1 year. Ultrasonography showed a hydrocele with multiple surface polypoid nodules. Subsequent computerized tomography (CT)-scan demonstrated a localized heterogeneous left scrotal tumour without evidence of local lymph nodes and abdomen involvement. Also, no metastatic dissemination in the cerebral or thoracic cavity was found. Laboratory blood tests were normal. The patient was a smoker, with an occupational history of asbestos exposure; he had worked as machines ship. Three months later the patient underwent left hemiscrotectomy with orchiectomy because the tumour was not separate from the left testicle. The patient underwent no further treatment until December 2010 when, at positron emission tomography (PET)-CT, multiple peritoneal nodules with enlarged lumbo-aortic lymph nodes were detected. Adjuvant chemotherapy was administered, consisting of three cycles of pemetrexed at 500 mg/m^2 and cisplatin at 80 mg/m^2, on day every three weeks (until April 2011). A partial response was obtained, but because of haematological toxicity the chemotherapy was stopped. The patient died of disease progression in June 2012 (18 months after recurrence, 44 months after surgery). On gross examination, the left orchiectomy specimen, measuring 10×7×5 cm, consisted of 3×2-cm testis, epididymis and, spermatic cord. It was covered by a translucent fibrotic wall. The internal surface showed a tumoral mass arising from the tunica vaginalis, and invading the testicular parenchyma (**Figure 1A**, **1B**).

Case 2

February 2006. An 82-year-old man, non-smoker and with no history of asbestos exposure, came to hospital with recurrent hydrocele. A trans-scrotal ultrasonography revealed very small multiple nodules measuring about 0.2-0.4 cm in size attached to the left parietal vaginal layer. He underwent hydrocelectomy and the pathologists reported a diagnosis of malignant mesothelioma. After 5 months a left radical orchiectomy was performed. Macroscopically the testis was normal and the tunica vaginalis showed some pedunculated nodules measuring 0.5 to 0.9 cm (macroscopic picture was not made). The patient refused external beam radiation therapy; disease progression appeared 53 months after surgery and exitus ensued (63 months after diagnosis).

Methods

The tumour samples were fixed in 10% buffered formalin and paraffin wax sections cut at 4 μm. Slides were stained with haematoxylin-eosin, Periodic Acid-Schiff with or without diastase-digestion and alcyan blue with or without hyaluronidase digestion. Selected blocks were processed for immunohistochemical analysis using the Envision Detection System (Dako, Denmark), DAB as chromogenic substrate and stained with the Dako Techmate automatic stainer after pre-treatment in a steamer at 99°C for antigen retrieval. Positive and negative control tissue specimens were used to evaluate antibody specificity. For immunohistochemistry, a wide panel of antibodies was used, including calretinin (DBA, Milan, Italy; 1:3000), cytokeratin 5/6 (Zaymed, San Francisco, California, USA; 1:100), human bone marrow endothelial (cell)-1 (Dako; 1:80), vimentin (Dako; 1:300), Ber EP4 (Dako; 1:500), Wilms' tumor gene 1 (WT49 clone, Menarini Laboratories, New-castle, United Kingdom, 1:20 dilution), monoclonal carcinoembryonic antigen (Dako; 1:25) and epithelial membrane antigen (EMA) (Dako; 1:75). Histologically, in both cases, examination of resected specimens showed a malignant mesothelioma arising from the tunica vaginalis and infiltrating adjacent structures such as the epididymis, with predominantly solid and tubular epithelial patterns (**Figures**

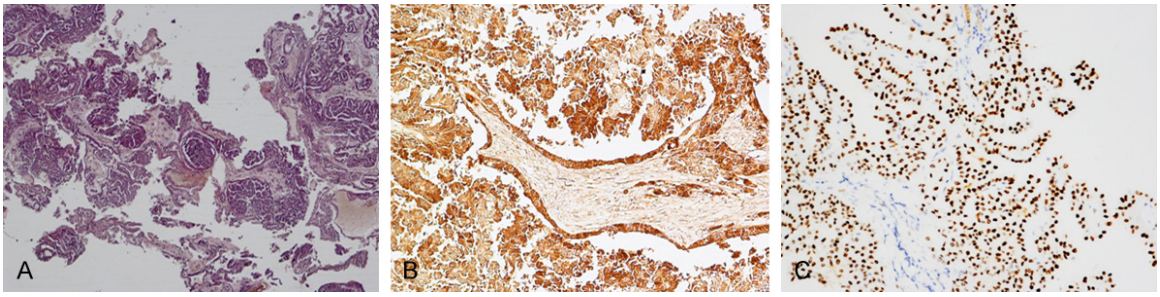
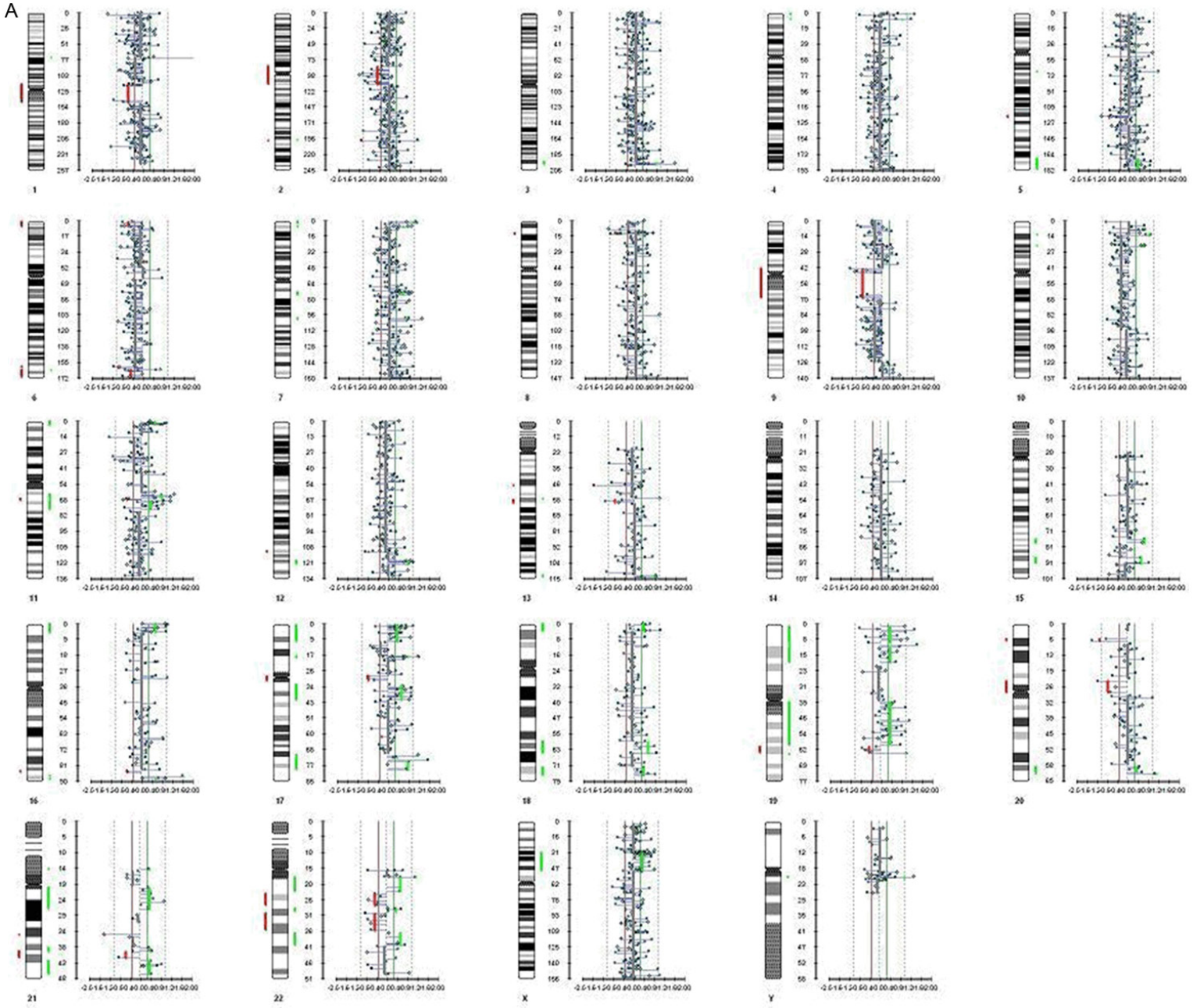


Figure 2. *Case 2*. (A) tubule-papillary growth pattern (HE, ×200). The tumor cells are strong positive for Calretinin (B) and WT1 (C) antibodies (×100).

1C, **1D**, **2A**). The neoplastic cells were generally polygonal, cuboidal or low columnar, with a pale to eosinophilic abundant cytoplasm. The degree of cells atypia varied from moderate to severe. Nucleoli were prominent and eosinophilic. Nuclear pseudo-inclusions and psammoma bodies were also seen. Mitotic figures ranged from 5 to 8 per 10 high-power fields (HPF) in *case 1* and 2 to 5 per 10/HPF in *case 2*. The stroma varied from oedematous to fibrous to mixoid. Foci of necrosis and vascular invasion were found in both cases. Nests of polygonal mesothelial cells were also seen, diffusely infiltrating the adjacent fibrous and adipose tissue of the skin (*case 1*). In both cases the tumour cells were immunoreactive to 5/6 cytokeratins, calretinin, WT-1 (only *in case 2*), HBME-1, EMA and vimentin antibodies (**Figures 1E**, **1F**, **2B**, **2C**).

Array-CGH studies

Informed written consent to the use of mesothelioma tissue for additional studies was obtained. Genomic DNA was extracted from 5-µm sections of paraffin-embedded tissue with the Dneasy Tissue Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Normal sex-matched DNA was extracted from peripheral blood lymphocytes according to standard hybridization procedures (Nucleon BACC3, Amersham Pharmacia Biotech, Bucks, UK). Array-CGH with a genomic resolution of about 0.5 Mb, increasing to 0.25 Mb in the subtelomeric regions, was carried out using the Cytochip V3 genomeARRAY slide (Techno Genetics Srl-Bouty Spa, Italy), containing 5.380 BAC clones, according to the manufacturer's instructions. Slides were scanned at 633 nm (Cy3) and 543 nm (Cy5) using the Scan ArrayGx (PerkinElmer, Waltham, MA, USA). Image analysis was done using BlueFuse software (Bluegnome Limited, Cambridge, UK). Once the positions of the biological sample were known, a powerful quantification algorithm was used to calculate the amount of signal at each spot location. For each clone, a $\log_2$ of the ratio Cy3/Cy5 fluorescent intensity was calculated. The raw results delivered by quantification were subjected to a series of post-processing stages including normalization, data exclusion, and identification of copy number change regions considering the replicate standard deviation values, the internal controls, the degree of confidence, and the median of the $\log_2$ ratio of clones in the regions. Data points lying beyond three standard deviations were considered to be part of a change analysis region. Regions exceeding the ratio thresholds of log 0.3 and log -0.3 and containing at least 1 clone were considered to be amplifications or deletions, respectively. The results of the experiments were visualized on the copy number panel. Full reports, including an ISCN summary of regions of change, were provided as Excel spreadsheets in the results directory. The analysis revealed many chromosomal abnormalities in both cases (**Figure 3A**, **3B**). DNA copy number changes detected are shown in **Table 1**. The total number of defects was 147 (81 gains and 66 losses) in *case 1* and 72 (50 gains and 22 losses) in *case 2*. The gains were largely concordant in both cases and more frequent than losses. Identical lost regions were at 1p13.3→q21.1; 19q13.42; 21q22.2; 22q12.2. Patient *1* survived 18 months after recurrence, while patient *2* survived for more than 4 years after surgery, and died 10 months after for disease progression, without chemotherapy.


A

B

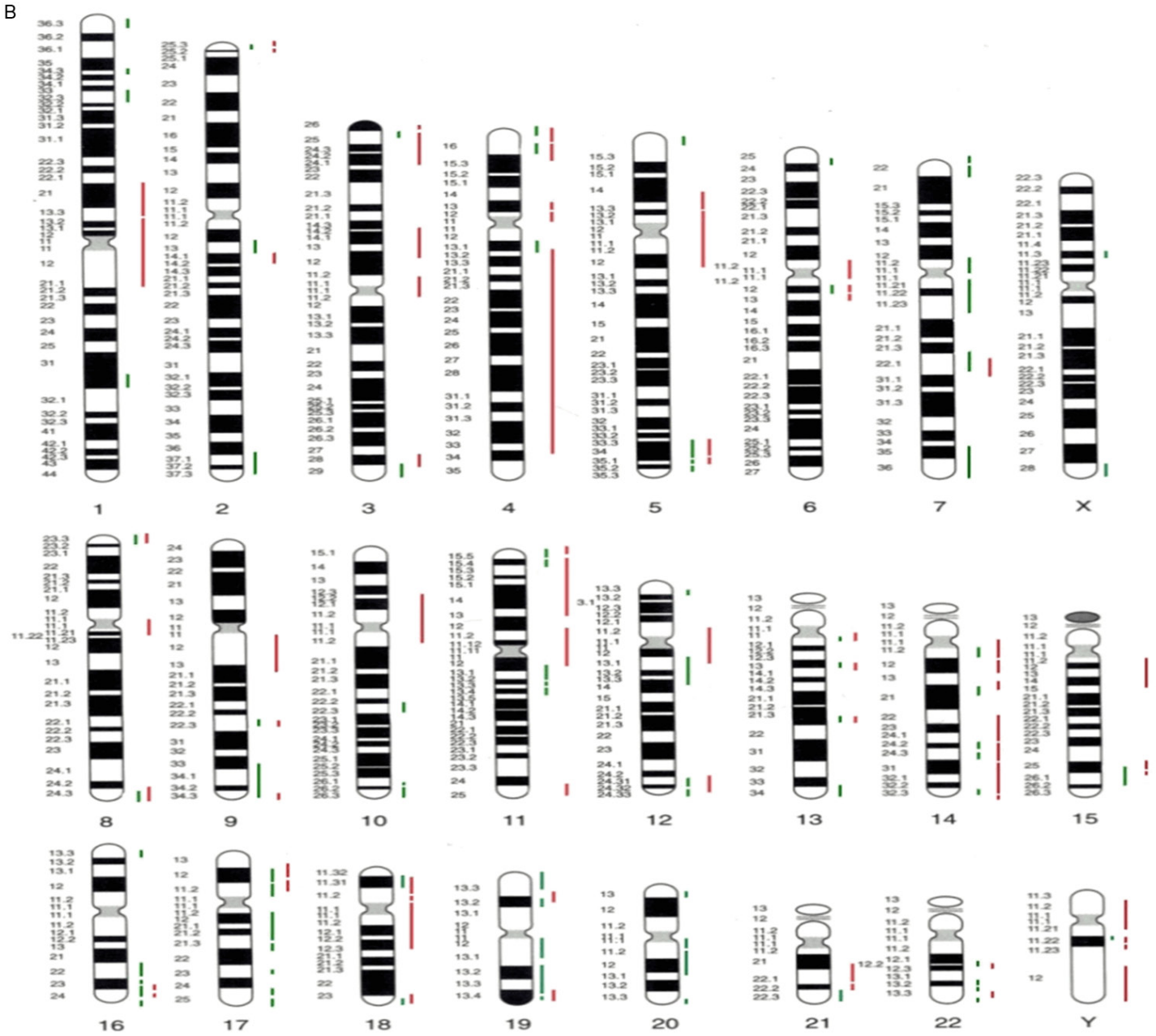


Figure 3. Copy number detected on microarray comparative genomic hybridization (a-CGH) in (A) *case 1* and (B) *case 2*. Red losses, green gains.

Table 1. Malignant mesothelioma of the testis: a-CGH results of reported cases. Identical losses are depicted in bold type

Case No.	Losses	Gains	Total losses	Total gains	Total defect
1	1p21.3→p13.3, 1p13.3→q21.1, 2p25.3, 2p25.2, 2q14.1, 3p26.1, 3p25.3→p24.1, 3p14.2→p12.3, 3p11.1→q11.2, 3q28, 4p16.3→p16.2, 4p16.1→p15.33, 4p13, 4p12→p11, 4q13.2→q34.1, 5p14.1→p13.3, 5p13.3→q12.3, 5q34, 5q35.1, 6p11.2→q11.1, 6q12, 6q13, 7q22.1, 8p23.3, 8q11.1→q11.21, 8q24.3, 9q12→q21.11, 9q22.32, 9q34.3, 10p12.2→q11.22, 11p15.5, 11p15.4→p13, 11p11.2→q12.2, 11q25, 12p11.21→q13.11, 12q24.31→q24.32, 13q11→q12.11, 13q13.3, 13q21.33, 14q11.1→q11.2, 14q12, 14q21.1, 14q22.2→q24.1, 14q24.2→q24.3, 14q24.3→q32.2, 14q32.33, 15q11.2→q14, 15q25.1→q25.2, 15q25.3, 16q23.3, 16q24.2, 17p12, 17p11.2, 18p11.31→p11.22, 18p11.21→q12.3, 18q23, 19p13.2, 19q13.41→q13.42, 21q21.3→q22.13, 21q22.2, 22q12.2, 22q13.32, Yp11.2→q11.21, Yq11.221→q11.222, Yq11.223, Yq12	1p36.33→p36.32, 1p34.3, 1p32.3, 1q31.3, 2p25.3, 2q13, 2q37.1→2q37.3, 3p25.3, 3q29, 4p16.3, 4p16.1, 4q13.1, 5p15.33, 5q34, 5q35.1, 5q35.2→q35.3, 6p25.1, 6q12, 7p22.3, 7p22.2→p22.1, 7p11.2→p11.1, 7q11.21→q11.23, 7q22.1, 7q35→q36.3, 8p23.3, 8q24.3, 9q22.32, 9q33.3→q34.3, 10q22.3, 10q26.13, 10q26.2→q26.3, 11p15.5, 11p15.4, 11q12.2→q13.2, 11q13.3, 11q13.4, 12p13.31, 12q13.11→q14.1, 12q24.31, 12q24.33, 13q12.11, 13q13.3, 13q21.33, 13q34, 14q11.2, 14q21.1, 14q24.2, 14q24.3, 14q32.32→q32.33, 15q25.3→q26.1, 16p13.3, 16q22.1→q22.2, 16q23.2, 16q23.3→q24.2, 16q24.3, 17p12, 17p11.2, 17q12→q21.31, 17q21.31→q21.33, 17q23.2, 17q25.1, 17q25.3, 18p11.31, 18q23, 19p13.3, 19p13.2, 19q12→q13.12, 19q13.2→q13.41, 19q13.42, 20p13, 20q11.1→q11.21, 20q11.21→q13.12, 20q13.33, 21q22.3, 22q12.2, 22q13.2, 22q13.31, 22q13.33, Xp11.3, Xq28, Yq11.221	66	81	147
2	1p13.1→q21.1, 2p11.2→q13, 2q33.1, 5q23.1, 6p25.3→p25.1, 6q25.3, 6q26 →q27, 8p23.1, 9p12→q13, 11q13.2, 12q24.13, 13q14.2, 13q21.2, 16q24.1, 17q11.2→q12, 19q13.42→q13.43, 20p12.3, 20p11.21→q11.1, 21q22.11, 21q22.2→q22.3, 22q11.23→q12.1, 22q12.2→q12.3	1p31.1, 2q33.1, 3q29, 4p16.3, 4p16.1, 5q13.2, 5q35.1→q35.3, 6q26, 7p22.3, 7p22.1, 7q11.23, 7q22.1, 10p13,10p12.31,11p15.5→p15.4, 11q13.1→q13.2, 11q13.3→q13.5, 12q24.23→q24.31, 13q21.1, 13q34, 15q24.3→q25.1, 15q26.1, 16p13.3, 16q24.2, 16q24.3, 17p13.3→p13.1, 17p11.2, 17q12→q21.31, 17q25.1, 17q25.1→q25.2, 17q25.3, 18p11.32→p11.31, 18q21.33→q22.1, 18q23, 19p13.3→p13.2, 19p13.2, 19p13.2→p13.11, 19q13.11→q13.42, 19q13.43, 20q13.33, 21q11.2, 21q21.1→q21.3, 21q22.2, 21q22.3, 22q11.21, 22q11.21→q11.23, 22q12.2, 22q13.1→q13.2, Xp21.2→p11.23, Yq11.221	22	50	72

Discussion

Intrascotal mesotheliomas are rare tumours, often discovered incidentally during hernia repair or after recurrent hydrocele or haematocele associated with diffuse thickening of the tunica vaginalis or the spermatic cord. To date, asbestos exposure is the only known risk factor. Most recurrences occur in the first two years after surgery and metastases have been found in inguinal and retroperitoneal nodes, abdominal peritoneum, lung, mediastinum, bone and brain [13, 22]. Because of the rarity of this neoplasm and its inauspicious diagnosis, a correct therapeutic protocol is still under discussion. Radical surgery is currently considered the best treatment for tumour localized in the scrotal site and chemotherapy combined with radiotherapy is administered after recurrence or metastasis. Cytogenetic and genetic molecular studies have demonstrated that most malignant mesotheliomas have multiple chromosomal alterations. Complex patterns of chromosomal aberrations have been detected and some recurrent chromosomal defects have been found and associated with an altered expression and activation or inactivation of critical genes in oncogenesis. Generally, chromosomal losses are more common than gains and a high frequency of homo-deletions is seen in 1p, 3p, 4q, 6q, 9p, 10p, 11p, 13q, 14q, 15q, 17p and 22q. Frequent gains are located at 1q, 5p, 7p, 8q, 11q, 15q, 17q and 20p. Deletions of several tumour suppressor genes, including NF2 (on 22q12), CDKN2A (on 9p21), BAP1 (on 3p21), LATS1 and LATS2 (on 13q12), WT1 (on 11p13) are implicated in the biology, diagnosis and prognosis of malignant mesothelioma [1]. Using the whole-genome array CGH strategy, we successfully identified a high total number

of chromosomal aberrations in the described cases of mesothelioma of the testis; losses were very numerous, especially in case "1". Also, in our study, the recurrent chromosomal changes are largely consistent with previous genetic analyses performed in advanced stages of mesothelioma and losses detected at 1p, 3p, 4q, 6q, 13q, 11p, 22q [18, 19, 23-26]. The lowest number of defects was observed in patients with a longer survival, not exposed to asbestos and who received only surgery. Losses in chromosomes 22q12.2, 19q, 1p13.1-p13.3 and 21q22.2 appeared to be the recurrent event in both cases, suggesting that they may be a common event in the tumorigenesis of MM testis.

Losses of chromosome 19 particularly in area 19p13 were present in asbestos-related cases; recently, this defect was found in many asbestos-induced cancers including mesothelioma [27]. WT1 was initially described as a tumor suppressor gene, but is now considered to perform oncogenic functions. Several studies have shown that WT1 gene expression is associated with different prognosis. In malignant mesothelioma WT1 expression is a good diagnostic marker but their potential prognostic value has not yet been established [1, 21, 28]. In accordance with Scattone *et al* [21] and Cedres *et al* [28], a loss of WT1 immunopositivity was observed in the patient's tumor with shorter survival. So, we analyzed 11p chromosomal defects and a loss at 1p13 was observed and this defect was correlated with loss of immunopositivity in the patient's tumor and shorter survival, suggesting an important prognostic role of WT1 in malignant mesothelioma.

22q12 was one the first tumor suppressor genes (TSGs) shown to be inactivated in MM; loss at 22q12 was observed in both patients, although they had a different disease progression and survival. In particular 22q12.2 contains the oncostatin M gene (OSM) which encodes a proliferation-inibiting cytokine [18]. A growth suppressive effect of OSM was documented for breast, melanoma, glioma, lung cancer and in many peritoneum mesotheliomas [18, 19, 29, 30]. The authors hypothesized that NF2 regulates the cell growth function and their inactivation could be related to tumor invasiveness and progression [18, 19].

In conclusion, the incidence of malignant mesothelioma is expected to increase in the near future. Although it is rare in the testis, it should be suspected especially in cases of recurrent epididymitis refractory to empirically effective antibiotic treatment. The diagnosis is confirmed by biopsies and radical surgery is currently recommended. Combined treatments may be necessary for patients with advanced stage disease [31]. However, the utility of chemotherapy and/or radiotherapy has not been clearly shown, since there are limited reported cases. Only one of the two patients who came to our attention received pemetrexed therapy after surgery. The problem is whether to combine ab initio orchiectomy and chemotherapy, and what are the criteria for this approach. We believe that genetic analysis is an additional diagnostic tool serving to confirm the diagnosis, as well as to assess biological tumour behaviour and aid the creation of personalized therapeutic strategies. A mesothelioma, localized but presenting a high number of genetic defects, could be submitted ab initio to a multimodal therapeutic treatment (sequential surgery, chemotherapy and/or radiotherapy) for the prevention of disease recurrence. Finally, to the best of our knowledge, NF2 expression has not been associated either with a specific type or site or with the prognosis of MM. The use of a-CGH makes it possible to identify profile DNA copy number changes typical of MMs, to recognize recurrent genomic imbalances implicating genes that may explain the aggressiveness of the tumour, and detect key points essential for the development of targeted therapies.

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Disclosure of conflict of interest

None.

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