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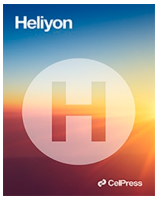

Case report

Newest therapeutic strategies impacting on rarest thoracic malignancies: The clinical case report of biphasic pleural mesothelioma

F. Pellicioli [a,b], L. Sala [a], F. Colonese [a], E. Belloni [c], M.I. Abbate [a], S. Canova [a], A. D'Agostino [a], D.L. Cortinovis [a,d,*]

[a] CS Medical Oncology, IRCCS San Gerardo Dei Tintori Foundation, Monza, Italy
[b] Department of Medical-Surgical Specialties, University of Brescia, Radiological Sciences and Public Health, Brescia, Italy
[c] CS Pathological Anatomy, IRCCS San Gerardo Dei Tintori Foundation, Monza, Italy
[d] Medicine and Surgery Department, University of Milano Bicocca, Milan, Italy

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ABSTRACT

A caucasian 62-year-old woman, diagnosed with biphasic pleural mesothelioma (PM) of II stage and BAP1 loss, was treated with therapies included in clinical trial and Early Access Programmes (EAP). During her clinical history, radiological images presented an unusual representation of the disease, with a pseudo progression discussed many times by several specialists. The patient's overall survival improved as a result of the multidisciplinary team and the availability of medicines outside of clinical practice.

1. Introduction

Mesothelioma is a rare cancer caused by an uncommon proliferation of mesothelial cells; PM is the commonest [1]. The incidence of PM is approximately 30 870 new cases per year in the world in 2020 [2]. There is a correlation between asbestos exposure and the onset of mesotheliomas; asbestos inhalation causes inflammation of mesothelial cells inducing proto-oncogenes activation. Smoking is not clearly associated with the onset of PM [3]. Data from the USA National Cancer Database for this patients report a median overall survival (OS) of 10 months [4]. According to histology there are three different subtypes: epithelioid, sarcomatoid/desmoplastic and biphasic mesothelioma. Immunohistochemical markers could be useful for differentiating the PM subtypes; sarcomatoid subtype is characterized by negative cytokeratin 5/6 whereas podoplanin and calretinin can be expressed in a variable percentage of cases, with calretinin being the more frequently positive marker [5].

Somatic mutations or deletions in BAP1 (variant of the BRCA1-associated protein 1 tumor suppressor gene) are expressed in mesothelioma in situ and represent a very early event in the development of mesothelioma's subset. The germline mutation of BAP1 appears to play a predisposition role to exposure-induced cancers [6]. BAP1 loss is less frequent in sarcomatoid mesotheliomas, and therefore, less helpful in distinguishing from benign processes [7]. The absence of specific biomarkers between different histological PM subtypes is challenging.

The disease can be divided into two groups: resectable and non resectable. In resectable disease there are two different surgical approaches: for the early stages pleurectomy/decortication, for the advanced stages extrapleural pneumonectomy. Even in selected

* Corresponding author. CS Medical Oncology, IRCCS San Gerardo Dei Tintori Foundation, Monza, Italy.
E-mail addresses: diegoluigi.cortinovis@irccs-sangerardo.it, diego.cortinovis@unimib.it (D.L. Cortinovis).

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cases, after multidisciplinary discussion, patients with early stage disease may be candidates for more radical surgery. The timing of surgical intervention can be evaluated after induction with platinum-based chemotherapy; however, a recent phase 3 trial demonstrated superior OS in patients who did not undergo surgery but received chemotherapy alone [8]; there is also the possibility to administer a "perioperative" treatment platinum-based which shows an improvement in progression-free survival (PFS) but not in OS [9,10]. Actually there is no data on the immunotherapy role in neoadjuvant/adjuvant therapies [11]. RT can be used after extrapleural pneumectomy, with poor results [3].

Immunotherapy, with a significant improvement in OS, is one of the many available first-line therapies for unresectable disease [12]. Cisplatin/carboplatin and pemetrexed chemotherapy are options for patients with contraindication for immunotherapy [13,14]. Also antiangiogenic drugs could have a role in first or second line therapy, as demonstrated by Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) and RAmucirumab MESothelioma treatment (RAMES) trials [15,16] Immunotherapy can also be used in second or subsequent line although the PROMISE-meso trial doesn't demonstrate an improvement in PRS or OS in pre-treated patients who received immunotherapy later [17–21]

After the introduction of immunotherapy, a new class of patients has appeared with the definition of long-term survivors also in poor prognosis population [22]. The case reported, characterized by a rare pathology with limited therapeutic options, highlights the importance of two aspects in managing this particular group of patients: the presence of a dedicated multidisciplinary team (MTD) [23] and the possibility of accessing treatments not necessarily included in clinical practice.

2. Case presentation

The patient reported was a caucasian 62-year-old former smoker woman diagnosed with biphasic PM characterized by BAP1 loss (II stage – cT1-2 N1M0) [24] and pleural effusion, with localization of disease at pleural nodes, pericardial, costophrenic and left mammalian lymph nodes. In her medical history there were gastroesophageal reflux disease, colon diverticulosis, surgical removal of breast's fibroma and hysterectomy due to uterine fibroma. No concomitant drugs were taken at the time of the diagnosis.

In April 2021 she started first line therapy with cisplatin (75 mg/mq) and pemetrexed (500 mg/mq) in association with 36 mg/mq pegargiminase (ADI PEG)/placebo in phase 2/3 clinical trial for six cycles [25]. After four weeks of treatment a computerized tomography (CT) scan revealed a partial response (PR) to the disease according to the modified RECIST 1.1 criteria for PM with persistence of para-aortic lymph nodes [26]. She continued clinical trial treatment but for creatinine increased grade 1, according to CTCAE Version 5.0 [27], she stopped cisplatin and started carboplatin (AUC 5). The CT scan at the end of chemotherapy reveals a PR, then she started the maintenance therapy with ADI PEG/placebo. The maintenance was stopped because the positron emission tomography (PET) scan and the CT scan revealed disease progression (PD) at para-aortic lymph nodes, between the lesser curvature of the stomach and the celiac tripod. The case was discussed by the MDT with confirmed radiological PD; there was no indication for radiotherapy.

After MDT consultation, she started second line treatment with immunotherapy (nivolumab 3 mg/kg and ipilimumab 1 mg/kg) in early access program (EAP). She developed an immune-related adverse event (IrAE) with hypothyroidism grade 2 and she started oral

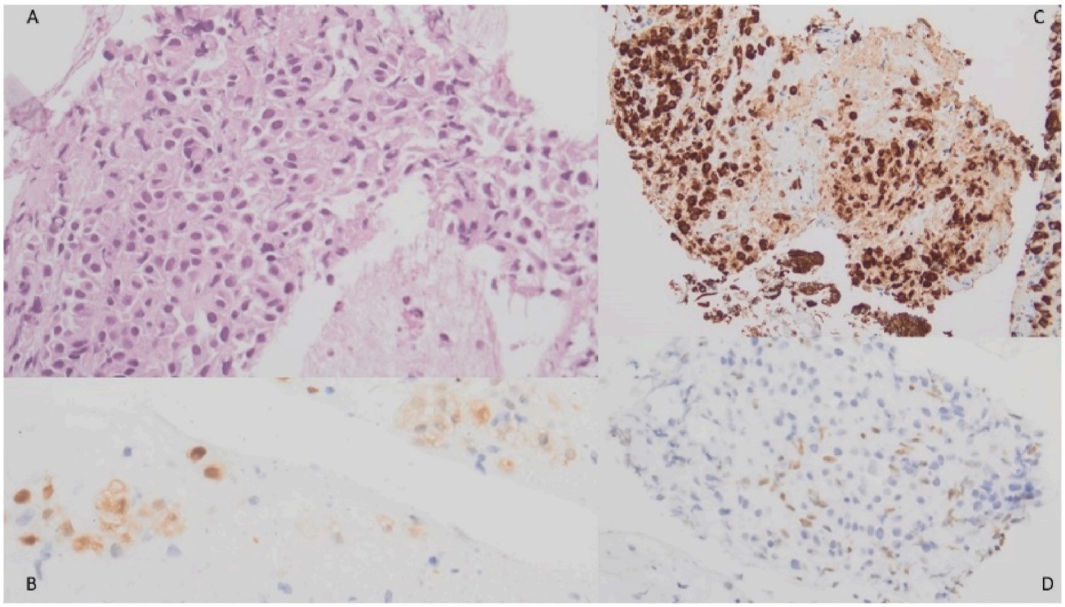

Fig. 1. Cell block from para-aortic node FNAB shows monomorphic epithelioid cell with mild atypia and solid architecture (A&E, 400x); immunohistochemistry: mesothelial cells react with calretinin (B, 200x), cytocheratin AE1/AE3 (C, 200x) whereas BAP1 is defective in this epithelioid mesothelioma (D, 400x).

therapy with levothyroxine 75mcg/die for a week, then 100 mcg/die. After two cycles the PET-CT scan revealed enlargement of the metabolic activity of a lymph node near the cardias and complete response (CR) of thoracic disease. Considering in differential diagnosis a lymph node activation secondary to immunotherapy versus lymph node disease progression, she underwent ultrasound endoscopy with biopsy, but the material was not adequate for a cytological diagnosis. The patient continued the therapy but she developed fatigue grade 1, myalgia grade 1 and hypoadrenocorticism grade 3; therapy with cortisone acetate 25mg was started. After this toxicity the brain MRI (Magnetic Risonance Imaging) revealed no evidence of inflammation or disease of pituitary gland; immunotherapy was stopped after 4 cycles.

She started follow up and at the PET-CT scan performed after 7 months, thoracic CR was confirmed. However, the PET scan after 11 months showed the increase of lymph node between celiac tripod and lesser curvature of the stomach as confirmed at the CT scan. She underwent another ultrasound endoscopy and the biopsy of suspicious lymph node confirmed the diagnosis of mesothelioma (Fig. 1A–D). The diagnosis of disease recurrence was made through a cytological examination, therefore the sample is limited. The presence of only the epithelioid component cannot represent the primary tumor. Since this is not a histological examination, it is not possible to define the distribution of the two components.

The patient started a third line therapy with gemcitabine (1000 mg/mq) in association with ramucirumab (10 mg/mq) in EAP; treatment was suspended after 6 cycles for intestinal obstruction requiring hospitalization. After progression of thoracic lymph nodes the patient was candidate for locoregional radiotherapy treatment. The patient then started a fourth line therapy with vinorelbine (30 mg/die) for 3 cycles, interrupted for general poor clinical conditions. The patient started home palliative care and died after one month (Fig. 2).

3. Discussion

PM is an insidious cancer. The physiopathology of this disease is challenging, there are different interactions between mesothelial cells and the immune system that have an important role in the natural history of mesothelioma [28]. Patients treated with Immune Checkpoint Inhibitors (ICI) had a longer duration of response and OS than patients treated by chemotherapy according to the results of Checkmate 743 trial; sarcomatoid and biphasic subtypes had greater relative benefits on OS than the epithelioid subtype [12]. The reason for this difference is certainly not proven. Programmed death-ligand 1 (PD-L1) expression could have a prognostic but not a predictive role; high PD-L1 expression of tumour cells independently is correlated with worse OS in PM [12]. In non-epithelioid histology, especially in sarcomatoid subtype, the expression of PD-L1 ($\geq$50 %) is lower and linked with a better prognosis than epithelioid subtype [29]. In this case, PD-L1 expression wasn't available, but the histological subtype as predictive factor of ICI response may explain the particular clinical behaviour.

Nivolumab and ipilimumab combination offers a new line of therapy that can positively impact on OS in patients with PM. Recently, the IND 227 trial and BEAT-meso trial also demonstrated that add pembrolizumab and atezolizumab respectively to chemotherapy in non resectable PM prolongs OS and reduces the risk of death [30,31]

Immunotherapy is effective in some cases but with costly adverse events, that could also lead to a definitive interruption; in literature up to 15 % of patients treated by double ICI stopped therapy for grade 3 or 4 toxicity [12]. On the other hand there is also a correlation between IrAEs and better OS; it has been shown that the onset of immunological toxicity is linked with a better response to treatment and prognosis. This correlation is explained by the hyperactivation of immune cells with a double function: a response towards self-cell and a response against the tumor. Not all European Union countries are allowed to use nivolumab and ipilimumab in epithelioid histology and or immunotherapy alone in further lines; this is an important limit interpreting the literature data to real world clinical practice. In our case access to therapies not included in routinely clinical practice represented a significant strategy to improve patient survival. Our multidisciplinary team many times needed to discuss especially how interpreter lymph nodes aspect: at first evaluation cardias lymph node looked like an inflammatory lymph node; only after some months did it look like a localization of disease with high glucose metabolism. Retrospectively, the lymph node near the cardias had always been a localization of disease that did no responde to any of the treatments used. This unusual representation of disease at imaging, with a possible pseudo progression, may be related to different patterns of response after immunotherapy, an aspect still debated in the scientific community [32,33]. For

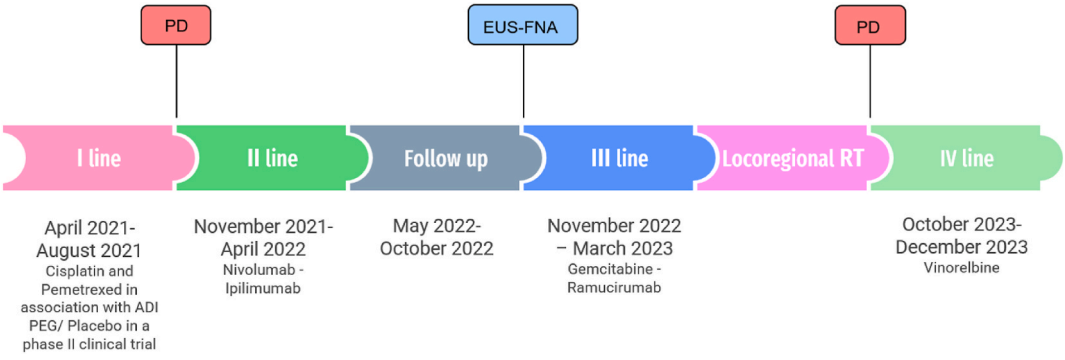

Fig. 2. Timeline.

this reason, it is of fundamental importance to expand the therapeutic options and at the same time ensure a multidisciplinary assistance to patients, in order to manage any critical issues.

4. Conclusion

The case here reported is a 62 years old woman with a biphasic pleural mesothelioma, a disease with a poor prognosis and limited therapeutic options. It is important to note that, thanks to therapies included in clinical trial, EAP and the MTD discussion, the patient lived for 36 months from diagnosis, more than three times the expected survival. This underlines the importance of guaranteeing equal access to therapies, including those outside clinical practice, from a multidisciplinary perspective, to allow an improvement in pathology response and quality of life.

Ethics statement

Written informed consent was obtained for the publication of all images and data.

Data availability statement

The data that support this clinical case are available from the corresponding author (DLC), upon reasonable request.

CRediT authorship contribution statement

F. Pellicioli: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization. **L. Sala:** Writing – review & editing, Visualization, Validation, Supervision, Data curation, Conceptualization. **F. Colonese:** Writing – review & editing, Visualization, Validation, Supervision, Data curation, Conceptualization. **E. Belloni:** Visualization, Validation, Data curation. **M.I. Abbate:** Writing – review & editing, Visualization, Validation, Supervision, Data curation, Conceptualization. **S. Canova:** Writing – review & editing, Visualization, Validation, Supervision, Data curation, Conceptualization. **A. D'Agostino:** Writing – review & editing, Writing – original draft, Visualization. **D.L. Cortinovis:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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