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Alternating chemotherapy with VDC-IE as effective first-line treatment in a patient with SMARCA4-deficient undifferentiated tumor

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Summary SMARCA4-deficient undifferentiated tumor (SMARCA4-UTs) is an extremely rare and aggressive entity where no consensus on systemic treatment exists to date. We report the case of a 43-year-old woman with thoracic SMARCA4-UT who presented with rapid progression of disease after surgical resection and achieved complete radiologic remission under VDC-IE chemotherapy (vincristine, doxorubicin, and cyclophosphamide [VDC], alternating with ifosfamide and etoposide [IE]). The detailed case report is followed by a brief discussion and overview of current literature.

Keywords Ifosfamide · Etoposide · Vincristine · Doxorubicin · Cyclophosphamide

Case report

In May 2023, a 43-year-old woman with a history of smoking (20 pack–years) was hospitalized due to pronounced dyspnea. Computed tomography (CT) of the chest showed right-sided pneumothorax with bullous disease and a mediastinal tumor with pericardial involvement (Fig. 1a); no distant metastases were detected. Uniportal video-assisted thoracoscopic surgery (uniportal VATS) with partial pneumectomy, bullectomy, and resection of pleural and pericardial lesions was performed, and the patient was subsequently discharged in stable condition.

Histological examination revealed an undifferentiated malignant tumor with mixed epitheloid and rhabdoid morphologic features and a high Ki-67 proliferation index of 90%. Immunohistochemical analysis showed a positive reaction for vimentin, CD34, and synaptophysin, as well as positive staining for BAP1, INI1, and MTAP; PD-L1 staining showed positivity of only 1% of tumor cells. Immunohistochemical reaction for SMARCA4 was completely absent, and a genomic assay confirmed the suspected diagnosis of a SMARCA4-deficient undifferentiated tumor.

Further analysis revealed high tumor mutation burden (TMB) with 14.9 mutations/megabase without evidence of microsatellite instability, as well as TP53 mutation. The tumor was staged as pT3, pNx, L0, V0, R0.

A CT scan carried out one month postoperatively revealed dramatic recurrence of the disease with malignant pleural effusion and tumor masses infiltrating the trachea, the descending aorta, and the right heart (Fig. 1b); no evidence of extrathoracic or osseous metastasis was present. The patient was admitted at our oncology department with worsening dyspnea, and repeated thoracenteses had to be performed. Thrombosis of the left subclavian vein further complicated the patient's clinical course.

Considering the aggressive histological phenotype and rapid progression of the tumor, a polychemotherapy protocol consisting of vincristine, doxorubicin, and cyclophosphamide (VDC), alternating with ifosfamide and etoposide (IE) was selected as first-line treatment. However, due to the patients' unfavorable condition and the considerable tumor mass, a primary dose reduction to 75% of maximal dose was deemed necessary.

Chemotherapy was administered as follows: for VDC, vincristine 1.13 mg/m^2 on day 1, doxorubicin

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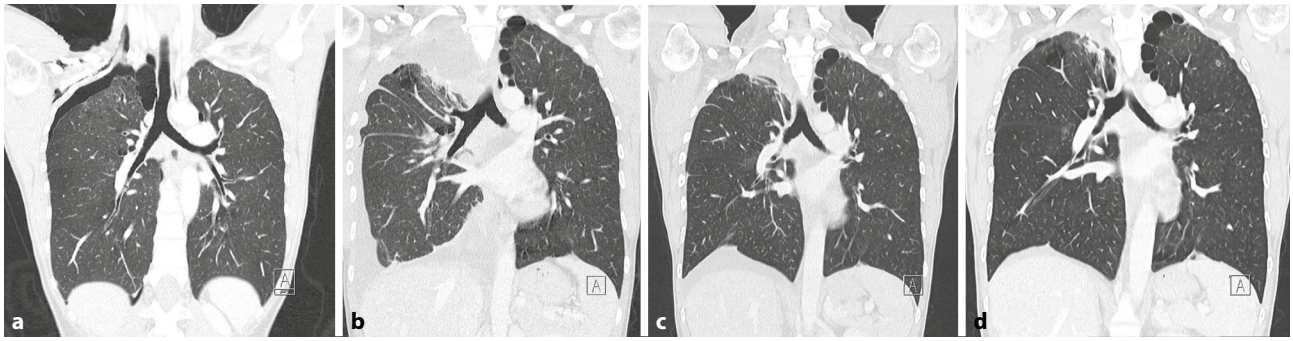

Fig. 1 Computed tomography imaging **a** at initial diagnosis, **b** at recurrence after resection, **c** partial response after six cycles of VDC-IE (vincristine, doxorubicin, and cyclophosphamide [VDC], alternating with ifosfamide and etoposide [IE]), and **d** complete response after eight cycles of VDC-IE (Comment: the consolidation in the medial part of the right apex was described as postoperative cicatrix)

28.13 mg/m^2 on days 1 and 2, cyclophosphamide 900 mg/m^2 on day 1; for IE, ifosfamide 1350 mg/m^2 on days 1–5 and etoposide 75 mg/m^2 on days 1–5. Chemotherapy was given every 2 weeks, and the patient received prophylaxis with granulocyte-colony stimulating factor (G-CSF) after each cycle.

Significant improvement of dyspnea was observed after the first two cycles, and no further thoracenteses were necessary. Chemotherapy was tolerated without complications and was able to be administered every 2 weeks as planned. After 6 cycles of chemotherapy, a restaging CT was performed, which showed remarkable response to therapy (Fig. 1c). Furthermore, a significant drop in levels of serum lactate dehydrogenase (LDH) was observed, from 821 U/L initially to 292 U/L at the time of restaging. Thus, treatment was continued, and after two further cycles of chemotherapy, a restaging CT showed no evidence of solid tumor, representing radiologic complete response (Fig. 1d).

Discussion

SMARCA4-deficient undifferentiated tumors (SMARCA4-UT) represent an extremely rare and aggressive malignancy associated with smoking and mainly affecting males. It is characterized by inactivation of SMARCA4, a gene encoding an ATPase subunit of the switch/sucrose nonfermenting (SW1/SNF) chromatin remodeling complex, which plays an important role in development, differentiation, and DNA repair [1]. Whereas SMARCA4-UT is associated with somatic mutation of SMARCA4, germline mutations of the gene are known molecular drivers of such malignancies as small cell carcinoma of ovary, hypercalcemic type, as well as malignant rhabdoid tumors in the context of rhabdoid tumor predisposition syndrome type 2 [2].

Histologically, SMARCA4-UT are poorly differentiated tumors, with epithelioid to rhabdoid cells with high mitotic rates. Furthermore, they are often located in the mediastinum, lung, or pleura. Prognosis is extremely poor, with median overall survival of approximately 7 months [3].

In the 2021 classification of thoracic tumors by the World Health Organization (WHO), SMARCA4-UT was defined as a stand-alone entity, distinct from SMARCA4-deficient non-small cell lung cancer (NSCLC) [4]. There have been various names for the disease in the past, such as SMARCA4-deficient thoracic tumor, SMARCA4-deficient thoracic sarcomatoid tumor, or SMARCA4-deficient thoracic sarcoma. This circumstance makes it somewhat difficult to research available literature. The terms “sarcoma” or “sarcomatoid” have been discarded based on detailed analysis of clinicopathologic, immunohistochemical, and genomic characteristics [5] and should thus be avoided by authors in future publications.

There is currently no consensus on optimal systemic therapy in SMARCA4-UT. Thus, as is often the case with rare entities, treatment regimens for more common tumors are implemented.

As mentioned above, SMARCA4-UT has previously been characterized as a sarcoma and—in some cases—treated as such. In a retrospective series of 30 patients who received diverse chemotherapy regimens, including vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) or doxorubicin, ifosfamide, dacarbazine, and mesna (MAID), therapeutic response was described as very poor, with a median overall survival of 6 months [6].

On the other hand, protocols analogous to non-small cell lung cancer (NSCLC) treatment have been implemented. For example, the combination of atezolizumab, bevacicumab, paclitaxel, and carboplatin was investigated in 3 patients with SMARCA4-UT. Two of the patients had high PD-L1 expression (40% and 80%), whereas the remaining patient had a PD-L1 score of 0%. Interestingly, all 3 patients achieved a partial response [7]. PD-L1 expression seems to have poor value as a prognostic marker [2].

In any case, therapy with immune checkpoint inhibitors (ICIs) is controversially discussed. Gantzer et al. described SMARCA4-UT as an “immune desert”,

referring to the lack of tertiary lymphoid structures (TLS) in a series of 9 patients, with the exception of one individual who exhibited TLS and was also the only patient in the series with response to ICI [8]. However, multiple publications view ICI as promising in SMARCA4-UT [9–11]. Most notably, Lin et al. reported impressive improvement in progression-free survival (PFS) with ICI plus chemotherapy vs. traditional chemotherapy as first-line treatment in a comparatively large series of 25 SMARCA-UT patients (26.8 vs. 2.73 months, $p = 0.0437$) [12].

As cases of SMARCA4-UT are so few and far apart, and in the lack of prospective data, treatment decisions are largely left to physician's choice. The rationale for selecting the VDC-IE protocol in the presented case is based mainly on our center's previous experience in implementing this regimen in other rare pulmonary malignancies, such as NUT carcinoma, as well as the general consideration of achieving rapid cytoreduction in a highly proliferative cancer.

Conclusion

To the best of our knowledge, this is the first report of successful treatment with chemotherapy with the VDC-IE protocol in a patient with SMARCA4-UT.

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Declarations

Conflict of interest P. Popov, O. Steinbrecher, A. Scharrer, M. Raderer, T. Brodowicz, M. Preusser and W. Lamm declare that they have no competing interests.

Ethical standards Statement of patient publication consent: We obtained the patient's informed consent to publish their clinical information and images.

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