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Consolidation Intensity-Modulated Whole Abdominal Radiotherapy as Part of the Complex Treatment for Metastatic Adrenocortical Carcinoma in Adolescence

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ABSTRACT

Adrenocortical carcinoma (ACC) is an extremely rare solid malignant tumor. We present rare local advanced ACC with lung metastases in adolescence. After visible radical surgery for a 100mm/130mm/50mm tumor, the initial histological diagnosis was anaplastic pleomorphic neuroblastoma originating from the left adrenal gland. Despite the eight courses chemotherapy, the disease progression was reported, which requires a pathohistological revision with a broad immunohistochemical (IHC) analysis. After surgical excision of peritoneal metastases, a system Ch alteration of Vincristine/ Cyclophospamide/ Farmarubicin and Vepesid/ Cisplatin - on 4 blocks each, in combination with the constant intake of Mitotane (Lesydren) was performed. Due to the disease progression, a consolidation intensity modulated radiotherapy (IMRT) of the right lung metastasis measuring 23 mm/ 16 mm with PET/ CT hypermetabolic activity/ SUV max 9,67 and of a vertebral L2 metastasis was performed. In December 2021, a right-sided thoracotomy with resection of three pulmonary metastases, followed by pulmonary segmentectomy of the irradiated right-sided lung metastasis was performed. The peritoneal metastatic dessimination necessitated a consolidation whole abdominal IMRT with boost in the tumor bed/ upper pole of the left kidney.

With this rare clinical case, we emphasize the role of complex treatment, especially with respect to local oncological therapy (surgery and IMRT) in metastatic adolescence ACC. Despite metastatic disease, complex treatment achieves a 3 -year survival rate.

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Introduction

Adrenocortical carcinoma (ACC) is a rare tumor, representing approximately 0.02% of all cancers [1, 2]. The incidence is believed to be 1 to 2 per million per year, but valid data is insufficient [3]. The main problem is that the ACC is extremely malignant locally advanced tumors, mainly diagnosed with lung (40%–80%), liver (40%–90%), and bone (5%–20%) metastases [4, 5]. The care for patients with rare diseases by the nonexpert is often based on extrapolation from other more common diseases or from the scarce evidence available through the medical literature [6]. The fact that 1.3% of all childhood cancers are ACCs as opposed to 0.02% to 0.2% of adult cancers confirms a higher relative incidence early in life [7-9].With this rare clinical case, we emphasize the role of complex treatment, especially with respect to local oncological therapy (surgery and radiotherapy) in metastatic ACC in adolescence.

Clinical Case

We present a 17-year-old girl with episodes of fever and left hypochondrium pain with a limitation period of October 2019. After the abdominal CT and FDG PET/CT, a left suprarenal mass with multiple pulmonary metastases was found. In April 2020, a visible radical surgery of a left adrenal gland tumor with a size of 100mm/130mm/50mm histologically judged for anaplastic pleomorphic neuroblastoma was performed. Following the surgery, 8 courses of adjuvant chemotherapy were appointed under the Rapid Cojec scheme from the protocol HR Neuroblastoma SIOP 2011. In October 2020, after the revision of the histological result, was estimated to be an undifferentiated adrenocortical carcinoma /G3 consisting of medium to large -sized atypical epithelial cells with high -growing pleomorphic nuclei, nuclear vacuoles, giant tumor cells, thin fibrous barriers between the conglomerates of tumor cells without mucus formation, but rich in PAS positive glycogen Immunohistochemical (IHC) analysis reports positive expression for Melan A (100%), Synaptophysin (50%), INSM1A8 (10%), Inhibin (10%), CK 8/18 (5-10%), KI 67 (25%), Calretinin (5%) and negative IHC expression for Chromogranin, Desmin and S100 Protein. PET/CT of November 2020 lack local recurrence, but bilaterally persist lung metastases. PET/CT January 2021- In the right lung, a 23 mm/ 16 mm nodular lesion with hypermetabolic activity- SUVmax 9.67 with a characteristic of pulmonary metastasis is visualized; in the third segment ventral lesion with a diameter of 10.5 mm x 7 mm /SUVmax 2.86; Two nodules in the 10th segment 8mm/7mm and 4mm with low-grade accumulation SUVmax 1.05; Metabolic active lesion in the body of L2 / SUVmax 5.94 suspect for bone

metastasis that is shown with a black arrow (Figure 1A). In the left adrenal bed, a soft tissue lesion with a diameter of 12mm x10 mm with hypermetabolic activity SUVmax 9.73 with a characteristic of local relapse is displayed. Lateral from the middle third of the left kidney at the level of its lower pole adjacent to the left small intestine, structures with hypermetabolic activity SUVmax 7.62 highly suspected for peritoneal lesions are visualized (Figure 1B). Intraoperatively in May 2021, in the abdominal cavity revision, there are three tumor formations laterally from the kidney respectively in the upper and lower pole and between them with the type of metastatic - whitish, short, easily bleeding with an irregular shape and size of about 3 cm. They are resected to healthy tissue. Two more metastases have been removed with the same characteristic. The histological result reports metastases from an anaplastic tumor corresponding to adenocortical carcinoma with tumor cell emboli in lymphatic and venous vessels. Post -operative treatment continues with systemic HT/ alteration of Vincristine/ Cyclophosphamide/ Farmarubicin and VepesidD/ Cisplatin - on 4 blocks each in combination with constant intake of Mitotane (Lesydren). PET/CT October 2021- Dorsal between the spleen and the upper third of the left kidney is again depicted with a soft tissue lesion with the radiomarker's supply fixation. The transitional described soft tissue lesion adjacent to the upper left kidney's upper pole has reduced metabolic activity SUVmax 6.06 (before SUVmax 9.73) with a local recurrence characteristic (Figure 2A/B). Right lung- slightly increased nodular lesion with a diameter of 25.5 mm x 18 mm with reduced metabolic activity SUVmax 3.41; ventral in the third lung segment nodular lesion with a diameter of 10.5 mm x 6.2 mm with a slightly reduced intensity SUVmax 2.2; the two nodules in the 10th lung segment with a diameter of 7.4mm/5.3 mm and 4mm without the radio marker accumulation; Metabolic active bone lesion in the body of L2/SUVmax 4.67 (Figure 3A/B). The girl was aimed at palliative radiation in the large right lung metastasis and in the solitary bone metastasis on a second lumbar vertebrae/L2. In November 2021, a consolidation IMRT by the VMAT method of the large right lung metastasis with daily dose (DD) 3 Gy up to total dose (TD) 42 Gy/ Biologically Equivalent Dose (BED) 50.4 Gy and of the bone metastasis/ a second lumbar vertebrae L2 with DD 2.7 Gy up to TD 38 Gy/ BED 43,1 Gy. (Figure 4). The child experienced a relatively good radiation treatment with leukopenia, which was controlled with leukocyte-derived growth factor.

In December 2021, a right -sided thoracotomy was performed with a resection of three pulmonary metastases in the lower and medium pulmonary, and in the second stage in January 2022 followed by the segmenttectomy of the irradiated pulmonary metastasis in the first segment. Histological result- metastases of low-differentiated adrenocortical carcinoma IHC analysis reports positive expression for Melan A, Synaptophysin, Inhibin and negative IHC expression for Chromogranin, S100 Protein, Cytokeratin AE1/AE3, CK 7 and TTF1. PET/CT April 2022/ 5 months after RT of the lung and bone metastasis and 3 months after the pulmonary surgery- The pulmonary metastasis in the upper lung of the right lung has a reduced volume of 20mm x15mm SUVmax 3.54; after the resection of the two metastases in the right pulmonary base, fibrosis was reported (Figure 5A). After the surgical resection of retroperitoneal metastases, between the spleen and the upper pole of the left kidney, a hypermetabolic area of the dorsal contour of the spleen SUVmax 4.47, suspected for residual metastasis, is displayed. In the surgery bed, hypodense structural changes with inhomogeneous accumulation SUVmax 4.23, at which residual tumor tissue cannot be excluded at the background are reported (Figure 5B). The tracked hypermetabolic lesion in the body of L2 has a sclerotic altered structure and with an increased in dynamics intensity SUV Max 8.09 / previous SUVmax 4.44 (Figure 5C). Presence of initial involvement of the liver with a metabolic active lesion in the eighth segment. The patient is directed for 1 course of the Etoposide/Cyclophosphamide scheme. Due to the peritoneal metastatic disease, the need for a consolidating postoperative RT of an entire abdomen with overdose in the areas of hypermetabolic activity on the dorsal splenic contour, as well as between the spleen and upper pole of the left kidney was evaluated. In May/ June 2022, we conducted an intensity modulated VMAT RT in the wall abdomen with a DD 1.5 Gy up to TD 15 Gy (Figure 6a, Figure 7). In the second stage, boost was carried out in the field with hypermetabolic PET/CT region, localized in the upper pole of left kidney, suspected for residual tumor tissue, with DD 2, Gy up to TD 30 Gy / TD sum 45 Gy (Figure 6b, Figure 8). The child experienced a relatively good radiation treatment with leukopenia, which was controlled with leukocyte-derived growth factor. After 2 months of the RT completion, the patient is subject to a control MRI of the liver, which is required for radiosurgery of the solitary liver metastasis.

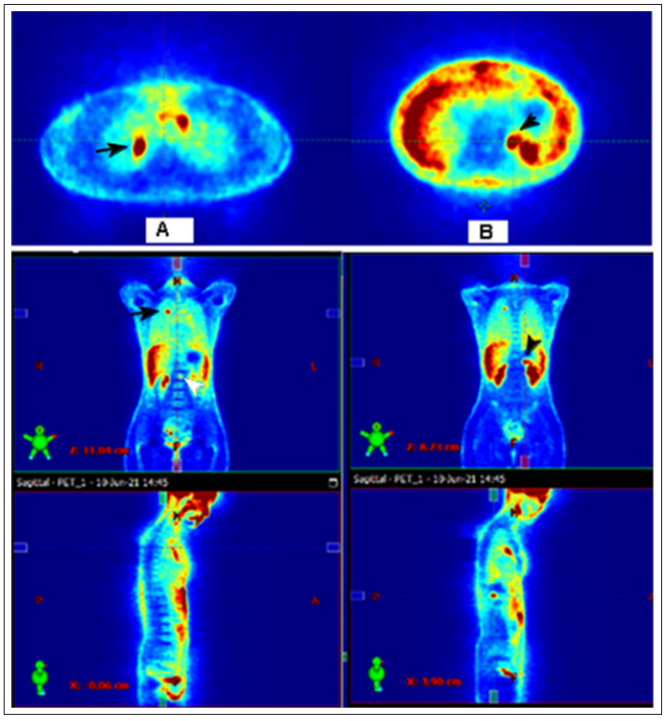

Figure 1: FDG PET/CT January 2021- A/ In the right lung, a 23 mm/ 16 mm nodular lesion with hypermetabolic activity- SUVmax 9.67 with a characteristic of lung metastasis; in the third segment ventral lesion with a diameter of 10.5 mm x 7 mm /SUVmax 2.86; Two nodules in the 10th segment 8mm/7mm and 4mm with low-grade accumulation SUVmax 1.05; Metabolic active lesion in the body of L2 / SUVmax 5.94 suspect for bone metastasis that is shown with a black arrow. B/ In the left adrenal bed, a soft tissue lesion with a diameter of 12mm x10 mm with hypermetabolic activity SUVmax 9.73 with a characteristic of local relapse that is shown with a black arrow. Lateral from the middle third of the left kidney at the level of its lower pole adjacent to the left small intestine, structures with hypermetabolic activity SUVmax 7.62 highly suspected for peritoneal lesions are visualized.

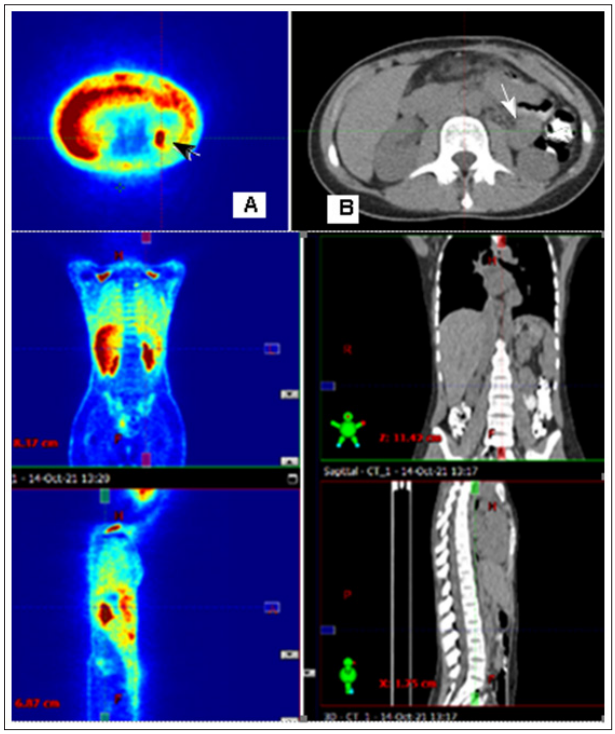

Figure 2: FDG PET/CT October 2021- A/ Dorsal between the spleen and the upper third of the left kidney is again depicted with a soft tissue lesion with the radio marker's supply fixation. The transitional described soft tissue lesion adjacent to the upper left kidney's upper pole has reduced metabolic activity SUVmax 6.06 (before SUVmax 9.73) with a local recurrence characteristic. The black arrow shows this formation. B/ CT image of the soft tissue recurrent lesion which is shown with a white arrow.

Figure 3: FDG PET/CT October 2021 A/ Right lung- Slightly increased nodular lesion with a diameter of 25.5 mm x 18 mm with reduced metabolic activity SUVmax 3.41; ventral in the third lung segment nodular lesion with a diameter of 10.5 mm x 6.2 mm with a slightly reduced intensity SUVmax 2.2; the two nodules in the 10th lung segment with a diameter of 7.4mm/5.3 mm and 4mm without the radio marker accumulation; Metabolic active bone lesion in the body of L2 / SUVmax 4.67 which is shown with a black arrow. B/ CT images- Nodular lesion with a diameter of 25.5 mm x 18 mm, which is shown with a white arrow.

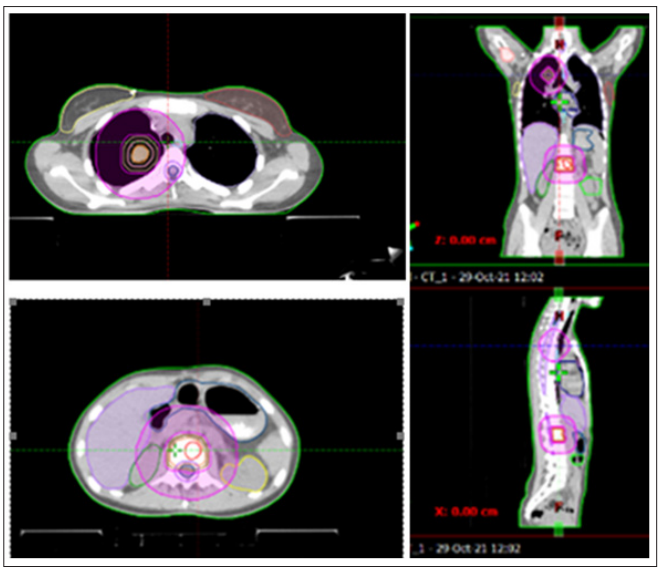

Figure 4: Contouring the targeted volumes and critical normal organs and tissues at RT of the large right lung metastasis and of the L2 metastasis / November 2021

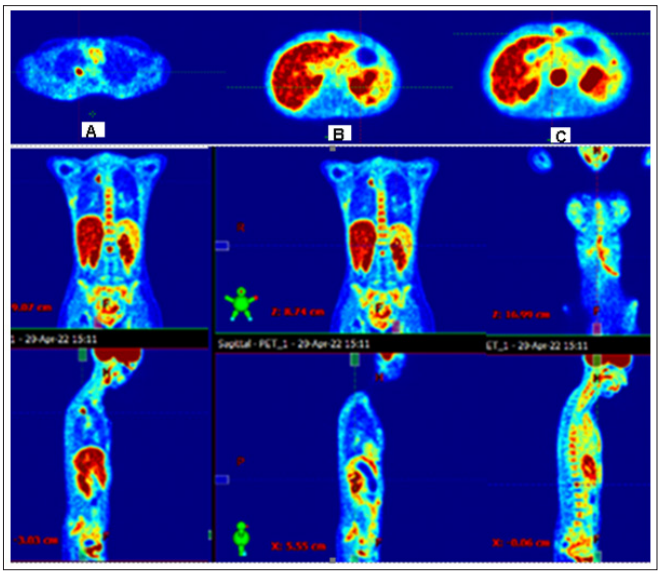

Figure 5: FDG PET/CT April 2022- 5 months after RT of the lung and bone metastasis and 3 months after the pulmonary surgery- A/The pulmonary metastasis in the upper lung of the right lung has a reduced volume of 20mm x15mm SUVmax 3.54; after the resection of the two metastases in the right pulmonary base, fibrosis was reported. B/ After the surgical resection of retroperitoneal metastases, between the spleen and the upper pole of the left kidney, a hypermetabolic area of the dorsal contour of the spleen with the SUVmax 4.47, suspected for residual metastasis, is displayed. In the surgery bed, hypodense structural changes with inhomogeneous accumulation with SUVmax 4.23, at which residual tumor tissue cannot be excluded at the background are reported. C/ The tracked hypermetabolic lesion in the body of L2 has a sclerotic altered structure and with an increased in dynamics intensity SUVmax 8.09 / previous SUVmax 4.44.

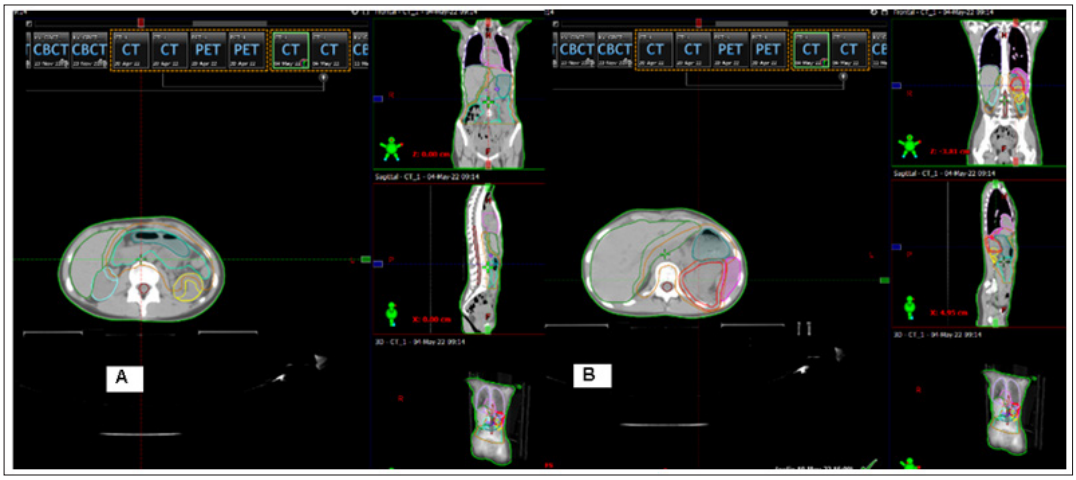

Figure 6: Contouring the clinical target volume (CTV) and critical normal organs A/ Whole abdomen with the exclusion of the pelvis. B/ CTV boost in hypermetabolic active residual tumor, localized at the upper pole of the left kidney /May 2022.

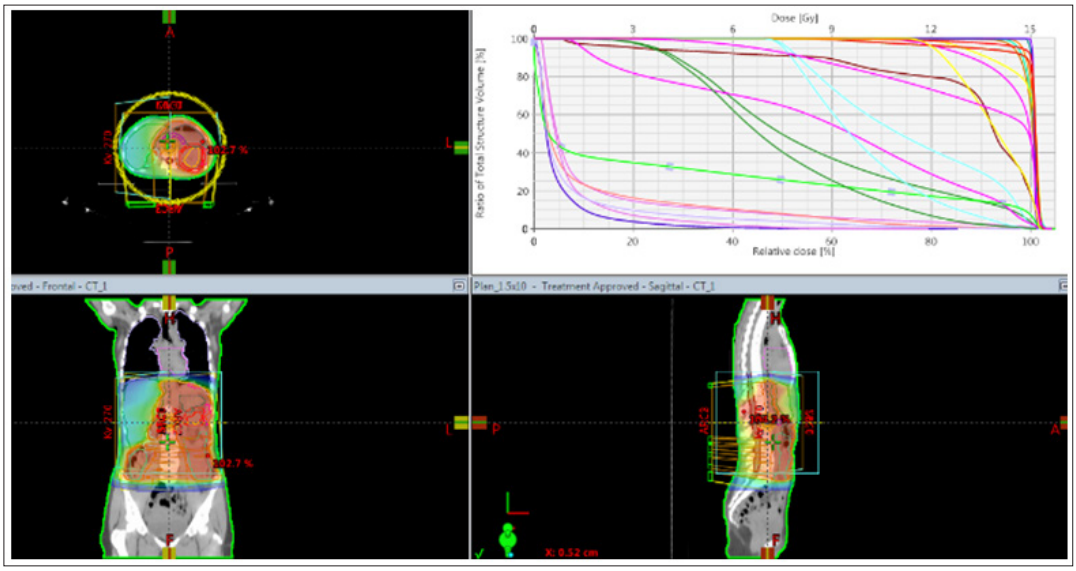

Figure 7: Intensity modulated RT by VMAT method in the abdominal cavity with DD 1.5 Gy up to TD 15 Gy. Histogram with dose distribution in target volumes and normal organs and tissue structures/ May/June 2022.

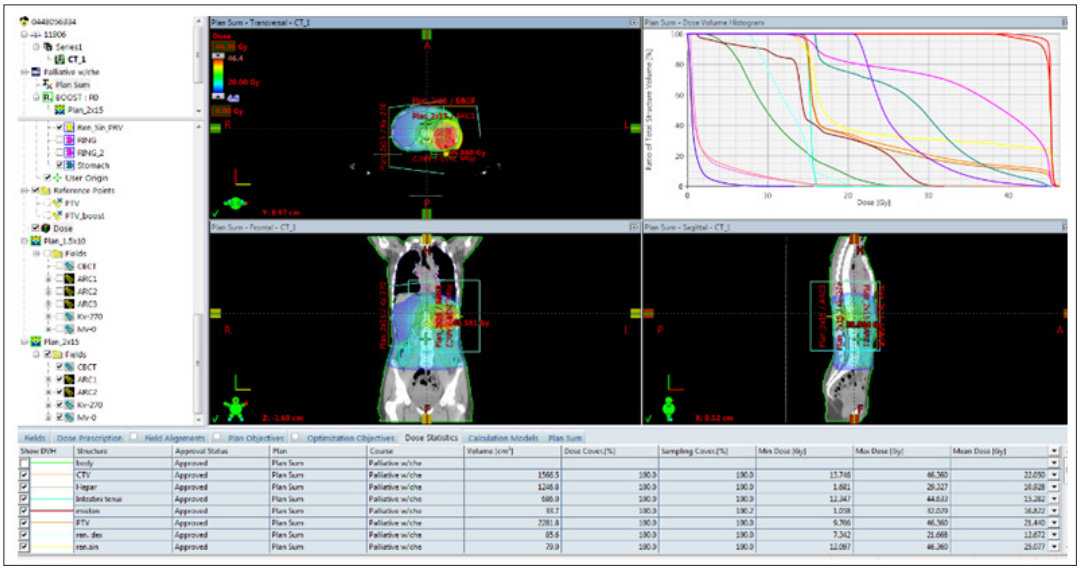

Figure 8: Intensity modulated RT for overdose/boost on hypermetabolic active residual tumor tissue, localized in the upper pole of left kidney with DD 2 Gy up to TD 30 Gy. The summary total dose in the tumor bed of the first and second RT is 45 Gy /May/June 2022.

Discussion

The National Institutes of Health Office of Rare Diseases Research defines rare diseases by a prevalence of fewer than 200 000 affected patients in the United States [10]. This definition categorizes the ACC to the extremely rare solid tumors, which are diagnosed mainly in the III and IV clinical stage. Non -specific symptoms are often observed involving abdominal or flank pain, abdominal fullness, or early satiety [11, 12]. At the time of presentation, ACCs are generally large tumors, measuring on average 10 to 13 cm such as the primary suprarenal tumor in our clinical case [13, 14]. With the presence of a questionable metastatic pulmonary nodule and large tumor of >4 cm, the clinical suspicion of malignancy was high in this case and favored radical adrenalectomy [15-17]. The precision pathohistological differential diagnosis of ACC in childhood requires a broad immunohistochemical (IHC) analysis. The following proteins are IHC expressed in most ACCs: Melan A, Synaptophysin, α-Inhibin and Calretinin [18-22]. In the clinical case presented, the positive IHC expression for Melan A (100%), Synaptophysin (50%), IM1A8 (10%), Inhibin (10%), CK 8/18 (5-10%), KI 67 (25%) and Calretinin (5%) proves the diagnosis and prevents confusion with neuroblastoma, which requires completely different therapeutic behavior. Tumor extent (eg, stage), specifically the presence of distant metastasis and number of organs involved in metastatic disease, confers a worse prognosis [23, 24]. Emerging evidence suggests that fluorodeoxyglucosefused positron emission tomography with CT (FDG-PET/ CT) is superior to CT alone [25].

Surgery should be conducted only after appropriate preoperative diagnostic tests, including biochemical evaluation and imaging. Due to the high probability of microscopic extension through the adrenal capsule, ACCs go unrecognized in the preoperative and intraoperative settings and hence highlight the importance of careful surgical technique including resection of all surrounding soft tissue and adjacent organs if necessary [26]. Recent recommendations by the American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons advocate open adrenalectomy by an experienced surgeon as the procedure of choice [27]. Although surgery is the treatment of choice for nonmetastastatic ACC, the decision for resection of the primary tumor in stage 4 disease needs to be individually addressed. Despite the poor prognosis in this patient group, chemotherapy has a limited role in the treatment of ACC, and surgical resection has been shown to have the best outcomes [28, 29]. Even with ostensibly complete resections, rates of local recurrence have typically ranged from at least 19% to 34% in those patients with no residual disease after surgery [24, 30]. In our clinical case, despite distant lung metastases, in a large locally advanced tumor with the inability of radical surgery, postoperative radiotherapy (RT) of the tumor bed was required. This could prevent local recurrences and peritoneal metastases of the tumor process. From the National Cancer Data Base, which found that 9% of ACC patients treated with surgery had microscopically positive margins (R1), whereas a further 10% had macroscopically positive margins (R2) [31]. For patients with an increased risk of local recurrence, eg, R1 resection with microscopic rests, radiation therapy to the tumor bed had long been employed [6]. Several studies have evaluated the efficacy of mitotane as an adjuvant therapy or for advanced ACC as a single treatment or in combination with chemotherapy [32, 33]. Single prospective studies examine the effectiveness of the combination of systemic chemotherapy with mitotane [34, 35]. The RT has been shown in several recent series to offer a significant improvement in disease control in both the adjuvant and palliative settings [36-39]. With our metastatic ACC after chemotherapy in combination with mitotan, there is a progression of both the suprarenal tumor with the expression of relapse and the pulmonary and peritoneal metastases and the growth of a solitary bone metastasis (Figure.1, Figure.2, Figure.3). Given the chemo- and radioresistance of ACC, we have conducted a palliative radiation of the large right pulmonary metastasis and bone metastasis of L2. It was the RT of the ACC that made us realize radical doses in order to control distant metastases. In November 2021, we have realized a consolidation IMRT by the VMAT method of the large right lung metastasis with daily dose (DD) 3 Gy up to total dose (TD) 42 Gy/ Biologically Equivalent Dose (BED) 50.4 Gy and of the bone metastasis/ a second lumbar vertebrae L2 with DD 2.7 Gy up to TD 38 Gy/ BED 43,1 Gy (Figure.4). In metastatic ACCs, surgical resections of the local relapse and peritoneal metastases are consolidating treatment that helps to achieve prolonged survival, but they should be followed by an adjuvant RT (Figure.5B). For the first time in the medical literature, we conducted an intensity modulated VMAT RT in the wall abdomen with a DD 1.5 Gy up to TD 15 Gy (Figure.6A, Figure.7). In the second stage, overdose/boost was carried out in the field with hypermetabolic PET/CT region, localized in the upper pole of left kidney, suspected for residual tumor tissue, with DD 2, Gy up to TD 30 Gy / TD sum 45 Gy (Figure.6B, Figure.8). The girl suffered a relatively good radiation treatment with leukopenia, which with leukocyte-derived growth factor was controlled. After 2 months of the RT completion, the patient is subject to a control MRI of the liver, which is required for radiosurgery of the solitary liver metastasis.

Conclusion

ACC in childhood and adolescence is an extremely rare solid malignant tumor. Pathohistological diagnosis requires a broad immunohistochemical analysis. For monitoring and restraining order of the metastatic ACC, PET/CT is required to report regression or progression of the disease. Given the chemo- and radio-resistance of ACC, we have conducted a palliative RT of the large right pulmonary metastasis and L2 bone metastasis. In metastatic ACCs, surgical resections of the local relapse and peritoneal metastases are consolidating treatment that helps to achieve prolonged survival, but they should be followed by an adjuvant RT. For the first time in the medical literature, we conducted a whole intensity modulated radiotherapy with an overdose/boost of the relapse bed. Despite metastatic disease, complex treatment achieves a 3 -year survival rate.

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