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RESEARCH ARTICLE

EVOLUTION AND THERAPEUTIC MANAGEMENT OF A AMELANOTIC MELANOMA WITH UNCOMMON LOCALIZATION - CASE REPORT

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ABSTRACT

This article provides information on the diagnosis of amelanotic melanoma in a young 40-year-oldpatientwith localization in the alveolar process of the 8th tooth of the lower jaw on the right side. During investigation and treatment for melanoma, the patient associates leiomyosarcoma at the tracheal level. Immunohistochemical markers specific for melanoma were found: S100, SOX-10. In leiomyosarcoma, immunohistochemistry reveals tumour cells positive for proteins normally found in smooth muscle cells, such as vimentin and smooth muscle actin (SMA). These markers are also positive in leiomyoma, but the histological features, in particular the uncontrolled cell division, the presence of atypia and necrosis support the diagnosis of leiomyosarcoma. The two primary tumours arise with secondary bone, brain and lung determinations. Since diagnosis and to this day, the patient has undergone surgery, immunotherapy, radiotherapy and chemotherapy. Although the patient's quality of life is currently unfavourable, with asthenia and fatigability, with difficulties in eating and speaking, given the extent of the disease, both loco-regional and systemic, the performance status is relatively good.

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INTRODUCTION

Amelanotic melanoma appears as a growth that does not contain melanin, a pigment found in skin cells, and contains stage I and/or II melanomas.(1)It is difficult to detect, as it has a reddish or pale pink colour, mainly due to DNA degradation of cells at that level. Other risk factors are chronic exposure to UV radiation and old age. The incidence of amelanotic melanoma is 2-8% of all melanoma cases. It often progresses into an invasive disease due to late diagnosis, and it frequently metastasizes rapidly, despite the small stage.(2).The immunohistochemical marker S100, identified since the early 1980s, is useful in the diagnosis of malignant melanoma(3), but the present findings suggest that the markers SOX-10 (Sry-related HMG-Box gene 10) and KBA 62 (Melanoma associated antigen) may also be useful, particularly in the diagnosis of amelanotic malignant melanoma.(4)SOX-10 is a transcription factor of the neural crest, and it is essential for the specification, maturation and maintenance of Schwann cells and melanocytes. The anti-SOX 10 antibody was applied to a variety of tumours derived from neural crest, mesenchymal and epithelial neoplasms, and normal tissues.

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Nuclear SOX10 expression was found in 76 out of 78 melanomas (97%) and 38 out of 77 malignant peripheral nerve sheath tumours (49%), while S100 protein was found in 71 melanomas (91%) and 23 malignant peripheral nerve sheath tumours (30%). SOX-10 was diffusely expressed in schwannomas and neurofibromas. SOX-10 reaction has been observed only in sustentacular cells of pheochromocytomas/ paragangliomas and occasionally carcinoid tumours in various organs but has not been observed in tumour cells. In normal tissues, SOX-10 was found in Schwann cells, melanocytes, and myoepithelial cells of salivary, bronchial, and mammary glands. SOX-10 reaction has not been identified in other mesenchymal and epithelial tumours, with the exception of diffuse myoepithelioma and astrocytoma. SOX-10 was expressed by metastatic melanomas and nodal capsular nevus in sentinel lymph nodes, but not by in other lymph node components such as dendritic cells. Our results indicate that SOX-10 will serve as a more sensitive and specific marker for the diagnosis of melanocytic and schwannoma tumours than the S100 protein.(5)

Case presentation: We present the case of a 40-year-old non-smoking patient with repeated dental infections, without significant comorbidities, originally from Ukraine, who in December 2021 is diagnosed with amelanotic melanoma of the alveolar mucosa.

Initially the lesion in the alveolar mucosa was electrically excised, subsequently the pathology report detected malignant peripheral nerve sheath tumour. Post-excision head and neck CT revealed secondary sumandibular and superior jugular lymph node determinations on the right side, cervical lymph node lymphadenopathy and main sinus polyp. The microscopic examination described small tumour fragments covered by squamous, multi-layered epithelium with signs of ulceration on the surface, elongated cells with eosinophilic cytoplasm, elongated, basophilic nuclei containing mitosis reactions, and thin-walled vessels between the tumour cell bundles. Histological changes differentiated melanoma without pigment from sarcoma. Immunohistochemistry was performed, showing specific melanoma markers: S100, SOX-10 and negative for cytokeratin. The maximum depth of the tumour in this sampled material was at least 2 mm. Subsequently, the patient underwent positron emission computed tomography with fluorodeoxyglucose (PET-CT), which reported single ipsilateral metabolically active nodes in the submandibular and carotid space (cN2 M0), with no evidence of systemic metastases. PET-CT was completed with brain MRI with contrast medium, without significant changes. Immunotherapy with Pembrolizumab was initiated in January 2021. Four doses were administered every three weeks. From January to May 2021, the patient performed imaging every 3 months, with no significant changes, no evidence of a tumour mass, and no nodes evident on previous PET-CT, being stationary. A nuclear magnetic resonance imaging of the brain, neck, soft tissues, and lower head was reinvestigated, which detected a formation of approximately 4 cm, heterogeneous structure, in the right projection of sinus 8 of the mandible. It was completed with CT scan of the head and neck with contrast substance with evidence of the same formation in the lower jaw on the right side with invasive growth.Staging was c T2 N2 M0, grade III. Subsequently, the patient presented to our oncology clinic with a good performance status, hemodynamically and respiratory balanced. An oral-maxillofacial surgery consultation was requested, which revealed locoregional recurrence and imaging investigation was recommended. The case was discussed in the oncology committee, a second opinion was opted for immunohistochemistry from the first surgery, BRAF mutation testing from tumour recurrence, then plastic surgery consultation was requested for surgery or oncology screening.A biopsy was taken from the tumour recurrence and the pathological examination concluded local recurrence of malignant melanoma.

Microscopic examination showed mucosa with squamous cells, in subepithelial stroma - atypical epithelioid cells, which are depleted on further sectioning. Double immunotherapy with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks was initiated. Following the interdisciplinary committee discussion, it was decided to administer IMRT-VMAT external palliative radiotherapy, 300 Cgy/fraction, up to a total dose of 39 Gy/right mandibular tumour volume and to continue immunotherapy. Brain MRI was performed with evidence of secondary determination. Gamma-Knife radiotherapy, 23 Gy on 53% is odose, was recommended, according to neurosurgery and radiotherapy consultations. External radiotherapy occurred with adverse reactions such as acute radio mucositis and acute radiodermatitis in the righ the mifacial, for which symptomatic treatment was recommended.

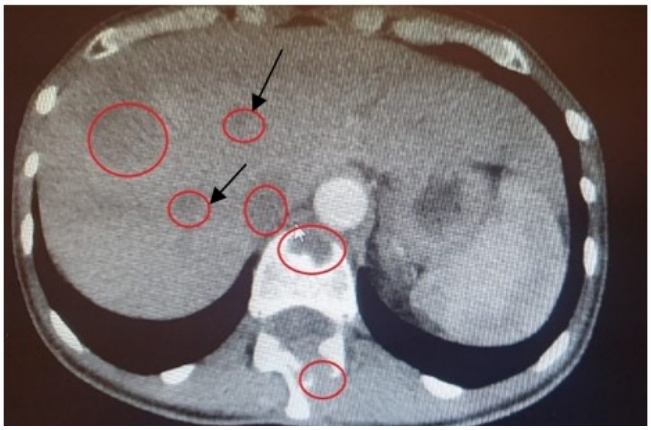

Fig. 1. Imagine CT-Liver and bone metastases are visible

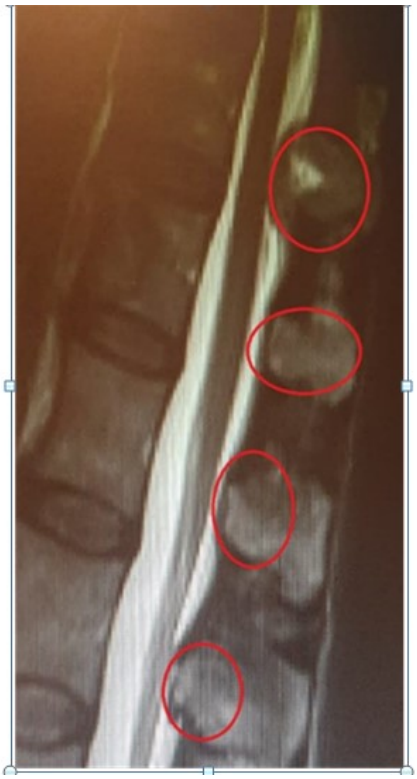

Fig. 2. Imagine CT-Vertebral osteolytic lesions

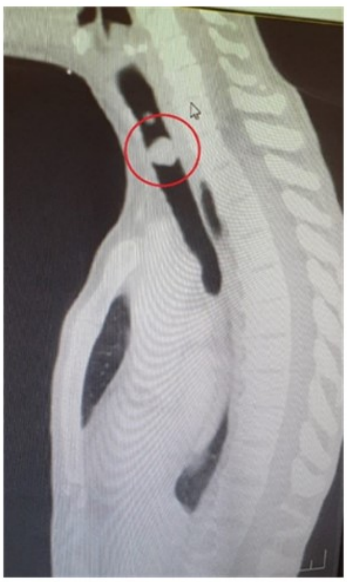

Fig. 3. Imagine CT-Tracheal formation

A total of 4 courses of immunotherapy with Nivolumab and I pilimumab were administered, then Nivolumab monotherapy was chosen, and 2 courses were administered. The patient presents clinically, enlarged tumour formation at the right hemifacial level, inability to speak, to eat, due to the tumour volume, dyspnoea, pain, and numbness at the right hemifacial level, thoracic and lumbar spine, moderate asthenia with fatigue, slight weight loss (4-5 kg) within 2 months.

On immunohisto chemistry: Cytokeratin AE1/AE3 positive in remaining squamous epithelium fragments, vimentin positive in tumour cells, SMA positive, CD 34 positive in vessels, negative in tumour cells, S 100 positive in tumour cells. Histopathological and immunohistochemical findings support the diagnosis of leiomyosarcoma. The case was re-discussed by a multidisciplinary team (oncologist, anatomopathologist, general surgeon, plastic surgeon,

Table A. Administered doses of chemotherapy

Pembrolizumab	4 dosesof 200 mg	q3w
Nivolumab+Ilpilimumab	4 dosesof Nivolumab 1mg/kg+ Ipilimumab 3 mg/kg	q3w
Nivolumab	2 dosesof 240 mg	q2w
Dacarbazine +Doxorubicin	2 dosesof Dacarbazine 750 mg/m2+ Doxorubicin 60 mg/m2	q3w

Table B. Irradiation doses at each target volume

Right mandibular tumour volume	External RT IMRT/VMAT	1 fraction/day, 5 days/week,300 Cgy/fraction, up to the total dose of 39 Gy
Secondary brain determination	Gamma Knife	23 Gy on isodose of 53%, target volume 9.75 cmc
Spinal bone volume (T11-T12)	External RT IMRT-VMAT	1 fraction/day, 5 days/week, 300 Cgy/fraction, up to the total dose of 30 Gy

Biologically, laboratory tests describe moderate anaemia, mild leukopenia, mild hepatic cytolysis, most likely due to immunotherapy administration.

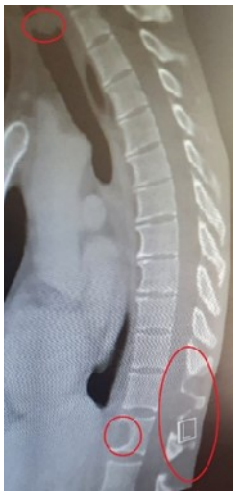

Fig. 4. Imagine CT-Tracheal formation and osteolytic lesions

Imaging reinvestigation revealed: a right submandibular tumorous bulky formation, with necrotic areas inside; a round, vegetating intraluminal tracheal lesion, approximately 1.5 cm in diameter, which creates a quasi-complete obstruction of the tracheal lumen, located in the cervical trachea (in front of the C7-T1 vertebrae);2 other small round vegetative intraluminal tracheal lesions of 0. 4/05 cm, right C6-C7 vertebrae, apparently with invasion at the left thyroid lobe; multiple bilateral secondary pulmonary findings, predominantly basal, osteolytic lesion at T11 vertebrae, with invasion at posterior epidural space, left lateral, with left T11-T12 neuroforaminal invasion and vertebral canal stenosis at this level and secondary hepatic finding of maximum 4.8 cm at segment VIII level. External radiotherapy was administered by IMRT-VMAT technique, 1 fraction/day, 5 days/week, 300 cGy/fraction, up to a total dose of 30 Gy/vertebral bone volume T11-T12. Corticosteroids were administered for mild relief of dyspnoea and bronchoscopy with biopsy was performed. Pathological examination described spindle-shaped cells arranged in bundles with atypical mitoses.

November 2022, chemotherapeutic treatment, compatible both in leiomyosarcoma and melanoma, with Dacarbazine Z1-4 750 mg/m2 continuous infusion for 96 hours, together with Doxorubicin 60 mg/m2 continuous perfusion for 96 hours, associated with granulocyte stimulating factor. So far, the patient has received 2 courses of chemotherapy, well tolerated.The patient presents with a good performance status, hemodynamically and respiratory balanced, with a slight visible shrinkage of the tumour formation in the right hemifacial area. Biological samples show no significant changes.

Conclusion

Although the patient tolerates the chemotherapeutic treatment well, the prognosis is unfavourable, considering the presence of the 2 primary tumours and the systemic extension. Imaging will be reinvestigated after 2 courses of doxorubicin and dacarbazine, with a total of 4 courses administered, as recommended by the specialist guidelines, and then discussed in a multidisciplinary committee to establish another treatment plan. We will try to obtain favourable results, as long as the patient's clinical condition allows us.

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