A Case Report of Adult Pineoblastoma Occurring in a Pregnant Woman

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Abstract. *Background/Aim: Pineoblastoma of the adult age is an uncommon tumor with only 200 cases reported. A standardized approach for an optimal adjuvant strategy is currently lacking. The case presented herein also deals with the issue of central nervous system tumors in pregnancy. Case Report: A 21-year-old pregnant woman presented with massive hydrocephalus due to a mass in the pineal region detected with MRI. After positioning an urgent ventricular derivation, a cesarean section was performed. During a third ventriculocisternostomy, a biopsy revealed a pineoblastoma. After a maximal safe resection, postoperative craniospinal irradiation for a total dose of 36 Gy plus a sequential boost to the tumor bed to 54 Gy, and adjuvant chemotherapy with CDDP plus CCNU plus vincristine were performed. After one year, the patient is alive with no evidence of disease. Conclusion: The use of adjuvant radio-chemotherapy provided excellent outcomes in our case. The advanced gestational age facilitated the choice of the therapeutic strategy.*

The suprasellar region is a rare site of intracranial tumors, accounting only for <1% of all brain neoplasms (1). Among the wide group of tumors occurring in this location, masses arising from pineal parenchyma represent only 0.3% of all central nervous system cancers (2). According to the updated 2016 World Health Organization (WHO) taxonomy (3) pineal neoplasms are categorized by histological grade in pineocytoma, pineal parenchymal tumor of intermediate differentiation, papillary pineal tumor and grade IV

pineoblastoma. All these tumors occur most frequently in pediatric patients, and are less common in adults. Usual clinical presentation is related to the obstruction of the sylvian aqueduct with consequent hydrocephalus and intracranial hypertension. Pineoblastoma accounts for 40% of parenchymal pineal cancers, and it represents the most aggressive subtype with a poor prognosis due to the frequent invasion of adjacent structures and cerebrospinal fluid dissemination, reporting 5-years survival rates <60% (4). The highest peak of incidence is described in the childhood, particularly in children less than 2 years old, where it can occur also in combination with retinoblastoma (5).

As mentioned above, starting from the second decade, adult cases are very rare and represent less than 10% of published literature (6). For this reason, limited data are currently available in the effort of developing a standard management of the disease, with a lack of consensus about the optimal combination of a multimodality treatment involving surgery, radiotherapy and/or chemotherapy. Here we report our case of a pineoblastoma occurring in a 9-months pregnant 21-year-old woman. Central nervous system tumors during pregnancy are rare, despite some histological subtypes that are specifically related to gravidity condition, like choriocarcinomas, pituitary benign tumors and meningiomas (7). In most cases, brain tumors display the same incidence in both pregnant and non-pregnant patients, but some authors have hypothesized that physiology changes related to pregnancy may influence the growth of intracranial masses both in terms of hemodynamic and of immuno-tolerance, with a potential more severe spectrum of symptoms at clinical presentation (8).

Consequently, pregnant patients represent a hard challenge in terms of management in the effort to provide an effective treatment keeping in mind the safety of the mother and the child.

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Case Presentation

After the recent onset of headache, nausea and dizziness with diplopia and difficulty in walking, a 21-year-old woman in a nine months state of pregnancy came at our hospital. A brain magnetic resonance imaging (MRI) revealed a triventricular hydrocephalus due to the presence of a contrast-enhanced mass in the pineal region (2.4x1.7x1.7 cm). The tumor appeared hyperintense in T2-weighted series and hypointense in T1 with colliquative features causing a massive compression on the mesencephalic aqueduct and an upwards stretch of the corpus callosum. After the positioning of an external ventricular derivation in urgency, a cesarean section was successfully performed. Afterwards, a cytology and MRI evaluation of the spine to assess the cerebrospinal fluid involvement were performed, with no evidence of dissemination. Due to the state of pregnancy, laboratory tests for α -fetoprotein and β -human chorionic gonadotropin were considered uninterpretable for the differential diagnosis process. The patient was a candidate to a third ventriculocisternostomy and a biopsy revealed the histological features of a grade IV WHO pineoblastoma. The subsequent maximal safe resection, using a supracerebellar infratentorial approach in sitting position, confirmed -on pathological examination- the grade IV WHO pineoblastoma with an intense mitosis activity, Ki67=70%, high nuclear-cytoplasmatic ratio and positive immunoreactivity for synaptophysin, CD56, chromogranin A.

A post-operative MRI of the brain and neuraxis performed after one month from surgery revealed the presence of a residual area of contrast-enhancement in the tumor bed, so the patient was candidated to an adjuvant radiotherapy treatment consisting of craniospinal irradiation with a sequential boost to the tumor bed. Radiation therapy was delivered with Image-guided Intensity Modulated Radiotherapy (IG-IMRT) by means of helical tomotherapy (Accuray Inc., Sunnyvale, CA, USA). Patient immobilization was obtained in the supine position with a head-neck-shoulder thermoplastic mask (Qfix Avondale, PA, USA) for the acquisition of a 2.5-mm slice thickness CT scan. Treatment plan was generated on the tomotherapy planning station, in order to deliver a total dose of 36 Gy in 20 fractions to the neuraxis plus a sequential boost to the tumor bed to reach a total dose of 54 Gy using 1.8 Gy fractions. Craniospinal target delineation was performed with the adoption of variable margins (isotropic 5 mm for brain and cervico-thoracic spine and isotropic 7 mm for lumbar-sacral spine) in order to compensate any positioning variability; for tumor bed boost, the target was delineated basing on preoperative and post-operative MRI image-fusion adding a 5-mm isotropic margin. Treatment delivery was administered with a daily verification of target coverage through the execution of megavoltage CT scans prior to each fraction. Our treatment was well-tolerated with no interruption

observed; the patient suffered only from occasional nausea and headache fully resolved after oral steroid therapy.

A brain and spine MRI performed after two months from the end of RT reported no evidence of disease. Subsequently, the patient started chemotherapy with CDDP plus CCNU plus vincristine. After one year from the end of treatment the patient is alive with no evidence of disease.

Discussion

To our knowledge, this is the first case of a pineoblastoma occurring in a pregnant woman, presenting two important issues of interest. First of all, the histological subtype, since pineoblastoma of the adult age accounts approximately 200 cases reported starting from 1979 (9). Consequently, it is hard to produce a standardized management of these patients, despite the role of surgery being established as a mainstay for all pineal parenchymal tumors (10), as the extent of surgical resection represents a crucial factor for its impact on survival (11).

Adjuvant radiotherapy is highly recommended, although the optimal dose and target volume still remain under debate. The largest experience of radiotherapy for pineal tumors is reported by Glanzmann *et al.* (12) who suggest a range of 44-50 Gy, keeping in mind that the authors referred to a 2D based radiotherapy. More recently, Kumar *et al.* (13) recommend a range of 50-54 Gy in conventional fractionation, preferably using newer techniques like IMRT, or at least 3D conformal RT. Concerning target volume delineation, despite the most common approach being based on craniospinal irradiation plus a local boost, some authors reported a focal treatment to tumor site alone: Lee *et al.* (14), evaluated 34 cases of pineoblastoma occurred in patients aged 16 years or more, including 24 subjects treated only with cranial radiotherapy, reporting that a cranial dose ≥ 40 Gy was associated with improved survival. However, the authors did not evaluate the choice of omitting neuraxis irradiation.

In our patient, adjuvant radiotherapy was performed with helical tomotherapy, a unique linear accelerator that integrates an IMRT helical system with a CT scan-based image guidance, offering the possibility to perform a daily verification in order to check setup positioning and adequate target coverage. Particularly for complex shape volumes, Helical Tomotherapy provides remarkable results in terms of avoiding junctions and gaps, organs at risk sparing and also gaining a more homogeneous dose distribution and target coverage (15).

Also, the role of chemotherapy is controversial and mainly investigated in paediatric patients (16-18), where pineoblastoma has a poorer prognosis (9). For adult patients, only limited data are available with inconclusive results (14, 19). Considering the biological similarity of medulloblastomas and pineoblastomas, for our patient adjuvant chemotherapy was proposed with CDDP plus CCNU plus vincristine.

Table I. Literature experiences of management of intracranial neoplasms in pregnant patients.

Authors (year)	N° of cases	Histological subtypes	Gestational age (weeks)	Craniotomy/delivery sequence
Beni-Adan <i>et al.</i> (21) (2001)	1	Neurinoma	35	After
Vougioukas <i>et al.</i> (22) (2004)	3	2 Glioma 1 Meningioma	23-33	3 Before
Annunziato <i>et al.</i> (23) (2005)	1	Hemangiopericytoma	40	After
Erickson <i>et al.</i> (24) (2005)	1	Rhabdoid tumor	30	Before
Simon <i>et al.</i> (25) (2005)	1	Hemangioma	38	Before
Ducray <i>et al.</i> (26) (2006)	3	2 Glioblastoma 1 Oligodendroglioma	12-29	Before
Bodner-Adler <i>et al.</i> (27) (2006)	1	Primitive neuroectodermal tumor	20	Before
Lynch <i>et al.</i> (28) (2010)	10	4 Astrocytoma	16-40	4 Before
		2 Meningioma		6 After
		1 Pituitary adenoma		
		3 Other		
Lee <i>et al.</i> (29) (2012)	1	Meningioma	28	Before
Verheeecke <i>et al.</i> (30) (2014)	27	10 Glioma	30-36	12 Before
		6 Astrocytoma		7 After
		2 Meningioma		2 No Craniotomy
		9 Other		2 Deceased
				4 Termination
Ravidra <i>et al.</i> (8) (2015)	1	Ganglioglioma	39	After
Kalbasi <i>et al.</i> (31) (2017)	1	Atypical theratoid/Rhabdoid tumor	14	Before
Present experience	1	Pineoblastoma	39	After

The other element of interest of the present report is the gravidity of the patient. Usually, the most frequent intracranial issues of pregnant women involve vascular pathologies, like arteriovenous malformations, cerebral aneurysms or preeclampsia-induced bleeding (20). Brain tumors are very uncommon during pregnancy and Table I (8, 21-31) collects the literature data about the other experiences of intracranial neoplasms in pregnant patients. In the present case, the state of pregnancy had a relevant impact on the differential diagnosis process, since the role of markers like α -fetoprotein and β -human chorionic gonadotropin was limited by the gravidity state. Also, as reported in a recent review by Ravindra *et al.* (8), some central nervous system tumors symptoms due to the intracranial hypertension may mimic a hyperemesis gravidum, making more challenging the diagnostic path. In this context, multidisciplinary management of pregnant patients represents a milestone to provide an effective treatment of the underlying disease and at the same time a safe delivery of the child.

The role of surgery is crucial, since the extent of resection is a consolidated positive prognostic factor, and can be safely performed during the second and third trimester of pregnancy (32). For patients with early gestational age, the choice of postponing surgery may be considered to reduce abortion risks, unless neurological symptoms require urgent intervention due to the mother's life-threatening condition. In our case, the patient was in advanced gestational age, but,

due to the presence of a massive hydrocephalus compressing mesencephalic structures, an urgent external ventricular derivation was mandatory. Once the patient was stabilized, the safe delivery of the child was performed with a cesarean section; afterwards, treatment strategy included the substitution of the external derivation with a third ventriculo-cisternostomy and a biopsy of the lesion, and, a week later, the surgical resection of the pineal mass was carried out.

The largest experience in the literature about the management of intracranial tumors in pregnancy is reported by Verheeecke *et al.* (30) in their series of 27 women, including also patients who received curative treatments (surgery, radio- or chemotherapy) during gravidity. Particularly, the authors describe the outcomes of 7 patients who received brain RT during pregnancy, stating that this treatment is safe for the fetus never exceeding the threshold dose of 0.1 Gy for the future child. However, in this series no patient received craniospinal irradiation. Bodner-Adler *et al.* (27) reported the case of a primitive neuroectodermal tumor in a pregnant woman in the second trimester managed with surgery and adjuvant brain radiotherapy during pregnancy, while neuraxis radiotherapy was postponed after the delivery at the 34th week of gestational age. Recently, Kalbasi *et al.* (31) reported the excellent outcomes of an atypical theratoid/rhabdoid tumor in a 25-year-old pregnant woman (14 weeks gestational age) who underwent surgical exeresis of the brain lesion and subsequently, at the 28th

week of fetal age, she received adjuvant proton beam craniospinal irradiation, with no evidence of recurrence and no late sequelae for the baby after three years of follow-up.

Conclusion

The advanced gestational stage of our patient facilitated the management of this rare tumor, since adjuvant therapies were safely performed after delivery. The integration of radiotherapy and chemotherapy after maximal safe resection revealed excellent outcomes. Since adult age pineoblastoma is under-represented in the literature more data are required to configure an optimal standard treatment strategy; particularly the role of chemotherapy should be further investigated.

Conflicts of Interest

The Authors report no conflicts of interest in this work.

Authors' Contributions

Study conception: Giuseppe Ferrera, Natale Francaviglia, Livio Blasi; Writing of the manuscript: Francesco Cuccia, Daniela Cespuglio, Gianluca Mortellaro; Data acquisition: Emanuele Quartuccio, Giorgia De Gregorio, Vito Valenti, Livio Blasi, Cristina Gallo; Literature review: Francesco Cuccia, Emanuele Quartuccio, Giorgia De Gregorio, Vito Valenti; Imaging evaluation: Cristina Gallo, Antonio Lo Casto; Manuscript supervision: Giuseppe Ferrera, Natale Francaviglia, Antonio Lo Casto. Final approval: All authors.

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