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Clinical report

Turner syndrome and meningioma: Support for a possible increased risk of neoplasia in Turner syndrome

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ABSTRACT

Neoplasia is uncommon in Turner syndrome, although there is some evidence that brain tumors are more common in Turner syndrome patients than in the general population. We describe a woman with Turner syndrome (45,X) with a meningioma, in whom a second neoplasia, basal cell carcinomas of the scalp and nose, developed five years later in the absence of therapeutic radiation. Together with 7 cases of Turner syndrome with meningioma from a population-based survey in the United Kingdom, and 3 other isolated cases in the literature, we review this small number of patients for evidence of risk factors related to Turner syndrome, such as associated structural anomalies or prior treatment. We performed histological and *fluorescent in situ hybridization* (FISH) of 22q (*NF2* locus) analyses of the meningeal tumor to search for possible molecular determinants. We are not able to prove causation between these two entities, but suggest that neoplasia may be a rare associated medical problem in Turner syndrome. Additional case reports and extension of population-based studies are needed.

1. Introduction

One in 2000 liveborn females is affected with Turner syndrome [Stochholm et al., 2006], a familiar sex chromosome abnormality in which there is an absent or structurally abnormal X chromosome, and less frequently, mosaicism [Bondy, 2007]. The well-delineated features of Turner syndrome include short stature, webbed neck, lymphedema, premature ovarian failure in infancy, left-sided cardiac anomalies, aortic dilation and dissection, renal malformations, otitis media and hearing loss, and multiple nevi [Bondy, 2007]. The risk for cancer in Turner syndrome traditionally focuses on the development of gonadoblastoma in women who carry Y chromosome material [Bondy, 2007]. However, a population-based survey [Schoemaker et al., 2008] noted various malignancies in this population, including an increased risk of central nervous system (CNS) tumors, also noted in case reports [Iacono et al., 1981; Kido et al., 1994; Nozza et al., 2005]. It is unclear whether these are coincidental, related to the absent X chromosome, or to the treatment of associated medical problems such as short stature, estrogen deficiency and reduced fertility. To further explore this association, we report a 44-year-old woman with 45,X Turner syndrome, bicuspid aortic valve, and pseudocoarctation, who delivered a child using oocyte donation-assisted reproductive technology (ART). She developed multiple meningiomas, required resection of a large right frontal meningioma, and subsequently developed basal cell carcinoma of the scalp and nose.

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2. Clinical report

2.1. Present history

A 44-year-old woman with Turner syndrome presented to an outside hospital with two brief episodes of altered mental status. A computed tomography (CT) scan of her head showed a 4.1-cm right frontal mass with surrounding edema, midline shift, sulbfalcine and uncal herniation, and hyperostosis of the sella turcica. She received high dose corticosteroids and an antiepileptic medication and was transferred to our emergency department. Neurological exam on presentation was only remarkable for a disconjugate gaze when looking to the left, but was otherwise non-focal. Abnormal laboratory values included a random glucose 161 mg/dL and alkaline phosphatase 136 U/L. The remaining tests were within normal limits, including electrolytes, renal function, thyroid function, prolactin, total and direct bilirubin, pancreatic enzymes, white blood count, platelets, and hematocrit.

Magnetic resonance imaging (MRI) of the brain showed a dural based, extra-axial, homogenously enhancing mass measuring 4.4-cm by 4.2-cm by 5.0-cm located in the right anterior cranial fossa, which extended across the midline, encased both carotid arteries, and invaded the cavernous sinuses. There was marked vasogenic edema in the right frontal and temporal lobes causing mass effect, compression of the right lateral ventricle, and 1.1-cm midline shift. Subfalcine and right uncal herniation was again evident. There was no evidence of infarction or hemorrhage, but the right anterior and middle cerebral arteries were displaced away from the mass. Detailed ophthalmologic exam showed chronic atrophic papilledema of the right eye and mild disc swelling of the left eye, indicating elevated intracranial pressure. She underwent subtotal tumor resection with right optic nerve decompression. There was bulky residual tumor along the skull base involving the left sphenoid wing, left cavernous sinus, prepontine space, and retroclival regions. Minimal residual tumor persisted along the right medial anterior temporal fossa and orbital apex. Postoperatively, she was maintained on high dose corticosteroids and antiepileptic prophylaxis. Her remaining neurological deficits after surgery include a non-reactive right surgical pupil, a third cranial nerve palsy with right ptosis and lateral deviation of the right eye, and mild reduced hearing in the right ear.

Pathologic review of the tumor specimen showed a meningothelial meningioma, WHO Grade I, with atypical features of sheeting and high cell density. Based on the low-grade histology and extensive radiation fields that would likely incur some late effects such as hypopituitarism, the patient declined adjuvant radiation therapy. The tumor was monitored with serial MRIs. Definitive fractionated radiation therapy of the meningioma was carried out over 5 years, with total dose field radiation of 57.8 Gy.

The patient then presented 5 years later with the development of a new vertex scalp lesion, which had grown over the past three months. The 2.6 cm lobulated lesion was mildly erythematous and slightly raised; the lesion correlated with MRI findings of an enhancing scalp lesion along the left scalp without clear evidence of erosion into the skull. She also was noted to have a smaller lesion of similar character on her nose. Biopsy of the scalp lesion revealed a 2.5 $\times$ 2.5 cm hyperkeratotic basal cell carcinoma, infiltrating type, which was resected at another institution. She had the lesion on the nose resected three months after the scalp resection at that same outside institution. Pathology of both lesions reportedly revealed findings consistent with basal cell carcinomas.

The meningioma bed at the time of the scalp basal cell carcinoma diagnosis showed subtle, but definitive interval increase in the size of the tumor nodule located near the inferior clivus. Although asymptomatic since her initial surgery, she experienced a generalized seizure two weeks after her scalp biopsy. Her antiepileptic medication, levetiracetam, was subsequently adjusted to reduce further risk of seizures. Two MRI scans performed in the sixth postoperative year have not shown increase in skull base tumor size, and possibly, a slight reduction. The patient had declined requests to have a CT angiogram of the aorta for more detailed monitoring.

2.2. Past medical history

The patient had been diagnosed with Turner syndrome as a newborn and received endocrinologic treatment in childhood. She was not aware of her chromosome complement until a karyotype was obtained during treatment for her meningioma. This showed 45,X in 10 out of 10 metaphases examined, excluding mosaicism greater than 26% at a 95% confidence limit. The patient had typical physical features of Turner syndrome with short stature (height 150 cm), multiple nevi, low posterior hairline, short neck with webbing (surgical scars on right), large and low set ears, subjective hypertelorism, down-slanting eyes, small chin, pectus excavatum, dysplastic toenails, and chronic lymphedema of legs. She was not known to have a congenital heart defect in childhood, and had a unilateral nephrectomy as a child for probable obstructive uropathy. She received growth hormone at age 10 years, and was treated for hypothyroidism since early adolescence. The patient also started hormone replacement therapy in late adolescence; which was not resumed after her first and only pregnancy. She did well academically in school without learning disabilities or extra services, attended junior college and subsequently nursing school. She reports red/green color-blindness. The patient reported frequent unprotected sun exposure in the summer (e.g. used baby oil instead of sun-blocking agents).

The patient married, and at age 35 years achieved pregnancy after several cycles of in vitro fertilization (IVF) with an anonymous egg donor. Her only biologic child was a male born at full term with multiple congenital anomalies. He had a normal chromosomal analysis, a right clubfoot, and bilateral ulnar deviation of the hands consistent with distal arthrogryposis (possibly consistent with Freeman–Sheldon syndrome by review of A.E.L.). He died at 6 weeks of age, which was attributed to Sudden Infant Death Syndrome (SIDS). There is no family history of known chromosomal abnormalities, birth defects, genetic syndromes (other than red/green color blindness), or brain or skin cancers. Her mother died of breast cancer at age 41.

Because of the detection of a heart murmur in the third trimester of her sole pregnancy, she had a cardiac MRI scan at another institution, which diagnosed a pseudocoarctation of the aorta (image not available for review). The most recent echocardiogram performed at another hospital approximately 4 ½ years after the meningioma was detected reported mild aortic regurgitation. The descending aorta was not described, and the aortic valve opened during this study, but was not well seen. The aortic root diameter was 2.9 cm (BSA 1.5 m^2).

2.3. Pathologic analysis of tumor

Fresh and frozen sections of the tumor revealed a meningioma with some atypical features. The H&E paraffin-embedded sections showed a meningioma of the meningothelial histological subtype (Fig. 1A). There were a few foci with moderately increased cell density. In some areas, tumor cells had an appearance reminiscent of “rhabdoid” features, with enlarged cells and eccentric nuclei (Fig. 1B). No other atypical features were present, (such as necrosis, prominent nucleoli, or increased nucleus–cytoplasm ratio) and mitotic figures were rare (<4/10 HPFs).