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Research Article

Rare Suprasellar Chordoid Meningioma with *INI1* gene mutation

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Abstract

Background: Chordoid Meningioma is a rare brain tumour characterized genetically by loss of genetic material from chromosome 22q at cytogenetic level resulting in mutation of *NF2* gene. **Objectives and case report:** In the present report, we described a rare case of suprasellar chordoid meningioma, which presented in a 32-year-old-woman. Her only complain was throbbing headache. Neurological examination showed left temporal hemianopia, decreased visual acuity (3/6), and no physical abnormalities related to Castleman syndrome were noted. Cranial magnetic resonance (MR) images demonstrated a 28x15 mm mass in the sellar region, which showed iso-to low intensity that enhanced vividly after gadolinium with upwards displacement of the Optic chiasm. Total surgical excision of the tumour was performed and subsequent histological examination of the tumour showed typical histology pattern of chordoid meningioma grade II according to the WHO classification system of meningiomas. Genomic DNA was extracted and mutation analysis for *INI1* gene using primer of exon 4, 5, 7, and 9 showed mutation involving exon 9. DNA sequencing showed heterozygosity C-T mutation in exon 9 of *INI1* gene leading to change of amino acid serine to phenylalanine at (codon 63). The details of this case are presented with a review of the literature.

Keywords: Chordoid Meningioma, Brain tumours, INI1 gene

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1. Introduction

Chordoid meningioma, accounts for 0.5% of all intracranial meningiomas. It was first described by Kepes et al., in 1988, and accepted as meningiomas variants by the WHO classification of the central nervous system tumour in 19931,2.

Association of the tumour with haematologic abnormality such as microcytic anaemia and dysgammaglobulinemia and/or Castleman syndrome have been repeatedly reported, especially, in paediatric patients [1], although chordoid meningioma with no hematological abnormalities have also been reported [3, 4].

Microscopically chordoid meningiomas have features of meningioma similar to chordoma which is usually characterized by epitheliod cord like tumour cells. It is classified as WHO grade II tumour [5]. There are eosinophilic vacuolated cells within a myxoid stroma and a lymphoplasmocytic infiltrate is often apparent and might be associated with haematological abnormalities [6].

Cytogenetic analysis revealed that monosomy 22 is a common, early, and perhaps primary event in the genesis of meningioma. Molecular analysis has identified several important candidate genes. Of those, Neurofibromatosis 2 (*NF2*), Tumour Suppressor in Lung Cancer-1 *(TSLC1),* and *TP53* are the most commonly reported.

The *INI1* (SMARCB1/hSNF5) gene, maps to chromosome 22q11.2, is part of the SWI/SNF complex participating in transcriptional regulation by remodeling chromatin in an ATP-dependent manner [7]. The SWI/SNF complex seems to be involved in DNA replication [8]. These features characterize members of the SWI/SNF complex as interesting targets for genes which may be involved in tumour formation.

Recently, *INI1* has been shown to carry mutations predominately in some central nervous system tumours such as meningiomas [9], schwannomas [10], astrocytomas11, ependymomas12 and glioblastomas11). *INI1*, therefore, is an interesting candidate gene for brain tumours, especially those entities that exhibit allelic loss on chromosome 22.

2. Material and Methods

2.1. The Case

A 32-year-old-female lady presented with four months history of throbbing headache and left visual field and acuity defect that worsened over the last three weeks. Neurological examination showed left temporal hemianopia, decreased visual acuity (3/6), and no physical abnormalities related to Castleman disease.

Routine laboratory investigations including Hb, MCV, MCH, total protein, albumen, and globulin were all normal. MRI revealed large iso-intense sellar mass measuring 2.8?1.5 X1.5 cm that enhanced vividly after gadolinium with upwards displacement of the Optic chiasm (Figure F1-A). A provisional preoperative diagnosis of a pituitary macro adenoma was made. Preoperative assessment of T3, T4, TSH and prolactin was normal. The patient was then operated upon through right sub frontal surgical approach. Intraoperatively, a firm, circumscribed fibrous tumour with numerous vascular feeders was found. Using the operating microscope, total excision of the tumour and its dural attachment was attained according to Simpson classification grade I13. Part of the tumour was fixed in 10% neutral formalin for histopathology examination. The other part was kept for molecular studies.

2.2. Molecular Analysis

Genomic DNA was isolated using chloroform phenol extraction methods. PCR was performed under standard conditions using dNTPs, Taq DNA polymerase (Promega, Madison, Wisconsin, USA), and a Biometra UNO Thermoblock (Biometra, Gottingen, Germany).

Primers of exon 4, 5, 7, and 9 for *INI1* gene, were analyzed by SSCP and direct sequencing employing a set of primers specified

Exon 4 forward primer, 5'-TCA GGT CCT ATA CTG ACT GG-3'.

Exon 4 reverse primer, 5'-AGA ACT AAG GCG GAA TCA GC-3'.

Exon 5 forward primer, 5'-GCT TCC ATT TCA CTT TCA GC-3'.

Exon 5 reverse primer, 5'-GTT CCC ACG TAA CAC ACA GG-3'.

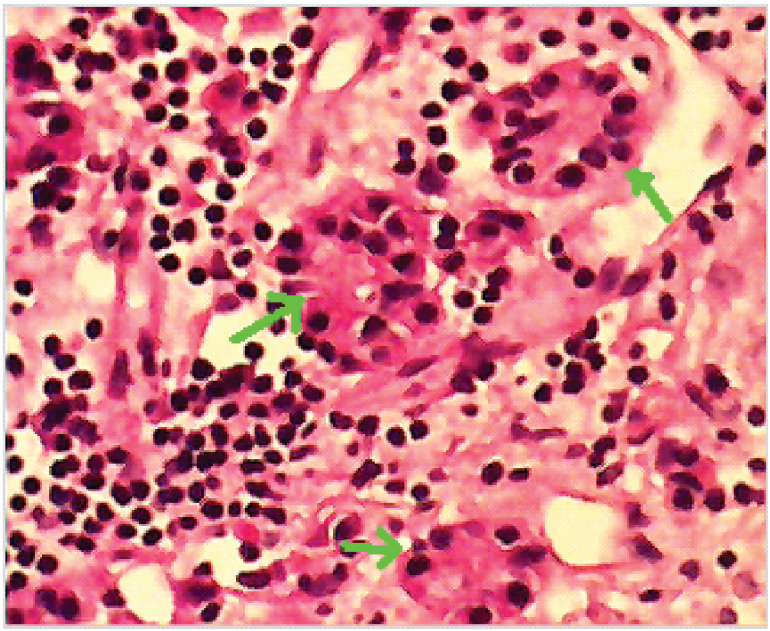
Exon 7 forward primer, 5'-CCTGGGCTGCAAAAGCTCTA-3'

Exon 7 reverse primer, 5'-GGAGGGAGAGACTCATGCAT-3'

Exon 9 forward primer, 5'-TGT TCC CAC CCC TAC ACT TG-3'.

Exon 9 reverse primer, 5'-ATG AAT GGA GAC GCG CGC TCT-3'

PCR was performed in a final volume of 25 μl containing 100 ng DNA, 50 mM KCl, 20 mM TRIS-HCl pH 8.4, 200 μM of each dNTP, 0.1% gelatin, 10 pmol of each primer, 1.0–2.0 mM MgCl2 and 0.25 U Taq polymerase. Using touchdown programmed initial denaturation at 94°C for 1 min was followed by 40 cycles on an automated thermal cycler (Biometra, Germany). These included denaturation at 94°C for 35 s, annealing at temperatures ranging from 58°C to 62°C depending on the primer pair for 40 s, and extension at 72°C for 40s followed by the final extension step at 72°C for 10 min. The



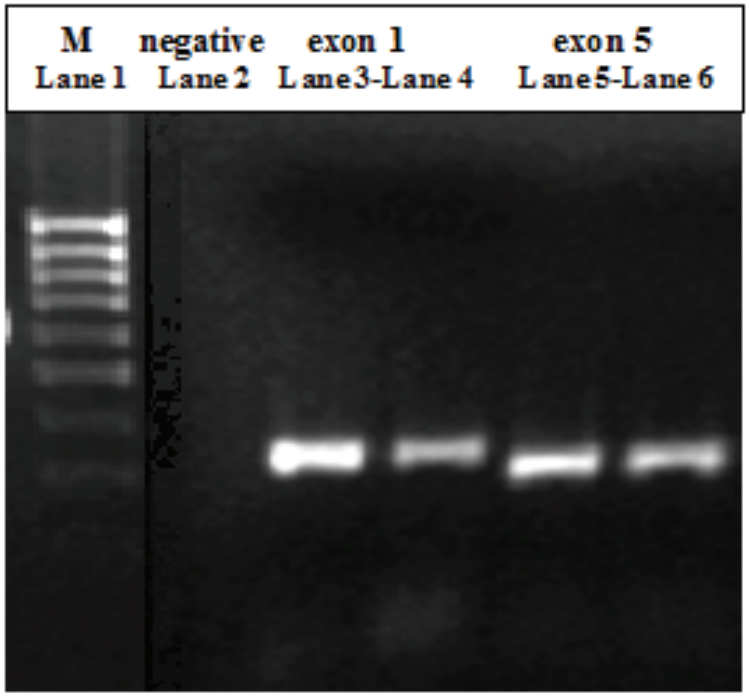


Figure 1

PCR products on acrylamide gel using SSCP analysis was performed on apparatus using 12% acrylamide gels. Electrophoresis was run at 2–6 W and variable temperatures.

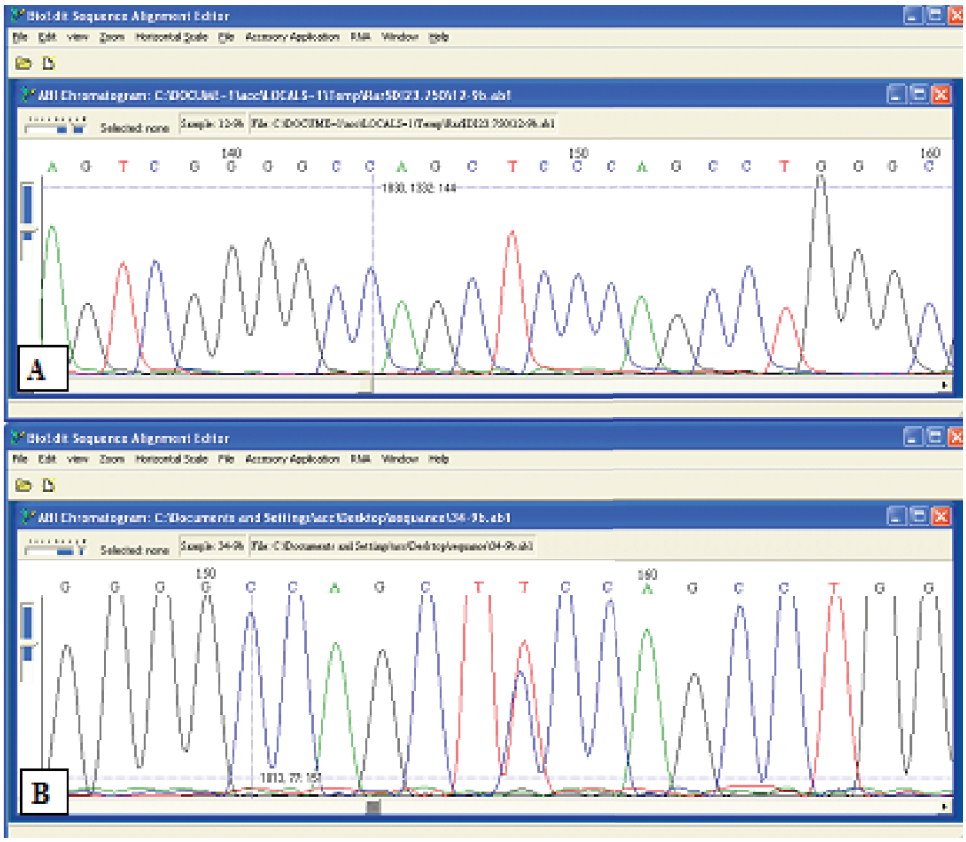


Figure 2

2.3. Sequencing

The same primers used for PCR analysis were used for sequencing. PCR products samples were sent for commercial sequencing at Macrogen, Seoul, Republic of Korea.

The BLAST (Basic Local Alignment Search Tool) programmer at the site of National Center for biotechnology Information (NCBI) was used for individual alignment of our samples.

3. Results

Following surgery the patient had an uneventful postoperative recovery; the headache subsided and the visual acuity markedly improved to 5\6. Postoperative values of T3, T4, TSH and prolactin were within normal ranges.

Microscopic examination of the tumour specimen revealed cluster of cohesive cells with dark regular nuclei and tapering cytoplasm arranged in a fibrous stroma showing an intense lymphocytic and plasma cells infiltration. There were scattered Russell bodies in the inflammatory reaction (Figure 2). The diagnosis of chordoid meningioma with

inflammatory reaction WHO Grade II was made and hence the patient was submitted to conformal radiotherapy [14, 15]. The postoperative MRI revealed total removal of the tumour (Figure F1-B).

3.1. Molecular results

The sequencing indicated that the mutation was heterozygotic with heterozygosity C-T mutation in exon 9 of INI1 gene, the mutation changed in the amino acid serine to phenylalanine in (codon 63) in this polymorphism data not reported in data analysis programmer.

4. Discussion

Schmitz and co-workers have suggested an important role of *INI1* gene in the pathogenesis of meningioma16. This suggestion led many to speculate that *NF2* is not the only important gene in the pathogenesis of meningioma17. However, *INI1* mutations were seen in only four tumours out of 126 meningiomas16. Interestingly, *INI1* mutations in all four cases were in the same position: nucleotide 377 (Arg to His substitution). This intriguing finding prompted others to check the status of *INI1* hot spots of exons 4, 5, 7 and 9 in meningioma. However, all these studies were based in Europe and USA, thus no such a study was performed in African population. Considering the differences in clinical, histopathological, and the natural history of meningiomas in the two populations, one may anticipate differences in the genetic profile as well.

Meningiomas can potentially occur at any site in the meninges. However, the most common locations known are the parasagittal and falcine tumours that account for around 24% of meningiomas, convexity tumours in 18%, olfactory groove, and tuberculer sellae seen in 10% each. Suprasellar chordoid meningioma is a rare tumour that may mimic pituitary adenomas. In the present case, the clinical presentation was dominated by headache and visual deterioration. The MRI finding was consistent with a pituitary adenoma. Association of chordoid meningioma and Castleman syndrome has been reported [18, 19]. The present case did not show features of Castleman syndrome.

Chordoid meningioma is a rare variant of meningioma; the differential diagnosis includes glioma, myxoid chondrosarcoma, chondroid chordoma, and other variants of meningiomas [4, 19–21]. Usually they show trabeculae or cords of eosinophilic vacuolated cells in myxoid matrix [22].

The fact that the tumour proved to be chordoid meningioma should alert attention to this possibility in interpretation of suprasellar tumours. More-over, WHO grade II

meningiomas are considered to have an aggressive course. In the present report, there were no features of an aggressive behavior; this might be due to early detection of the tumour. The aggressive behaviour and the fibrous texture of these tumours with its close anatomical relation to the vital structures in the sellar region render tumour recurrence a potential risk. Use of post-operative radio therapy lessens the chance of recurrence. Close and regular follow up of these patients is mandatory to detect such recurrence. conclusion: The general belief from the clinical point of view that meningiomas are benign tumours has to be accepted with great care, since only the histological diagnosis can verify the potential aggressive behaviour of the tumour and the subsequent liability for recurrence.

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