A Rare Case of Glioblastoma Multiforme in Association with Alkaptonuria and Ochronosis

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INTRODUCTION

Glioblastoma multiforme is a primary brain neoplasm, consisting of a genetically and phenotypically heterogeneous group of tumours.[1] The term glioblastoma multiforme (GBM) was introduced by Cushing in the second half of the nineteenth century, while the first operation on a patient suffering from this type of tumour was conducted in Vienna in 1904[1]. Ninety percent of glioblastoma multiforme cases develop de novo (primary glioblastoma) from normal glial cells by multistep tumorigenesis.[1] The remaining 10% of gliomas are cases of secondary neoplasm, developing through progression from low-grade tumours (diffuse or anaplastic astrocytoma's), which takes about 4–5 years.[1] Secondary glioma is diagnosed mostly in persons with the mean age of 39 years, grows more slowly and has a better prognosis.[1] Glioblastoma multiforme, which develops de novo, grows within 3 months.[1] Although the genetic basis, as well as the molecular pathways underlying development of primary and secondary gliomas are different these two types show no morphological differences.[1]

Alkaptonuria is an ultra-rare (1:250.000–1.000.000 incidence) autosomal recessive inborn error of catabolism of the aromatic amino acids' phenylalanine and tyrosine due to a deficient activity of the enzyme homogentisate 1,2-dioxygenase. This leads to the accumulation of homogentisic acid (HGA, 2, 5-dihydroxyphenylacetic acid).[2] HGA oxidizes to benzoquinone acetic acid (BQA), which in turn forms melanin-based polymers, deposited in the connective tissue of various organs, causing a pigmentation known as ochronosis, leading to dramatic tissue degeneration.[3] A severe form of arthropathy is the most common AKU clinical presentation.[4]

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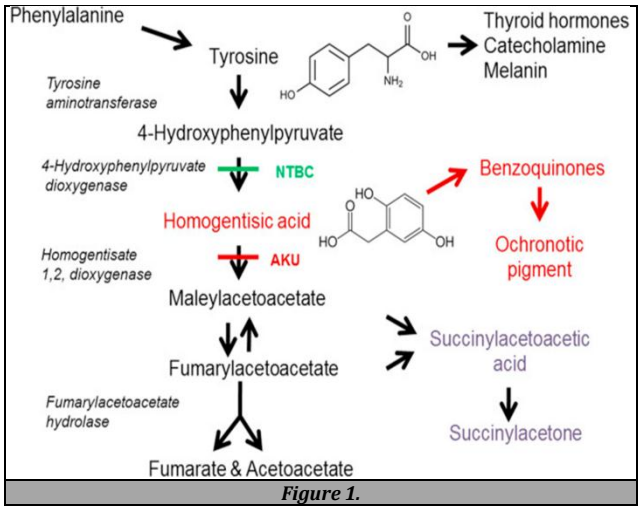

Figure 1.

PRESENTATION OF CASE

A 55-year-old male patient came with a history of seizure – had olfactory aura (foul smell sensation) followed by tonic posturing of limbs and loss of consciousness with tongue bite, persistence of foul smell aura even after medication of anticonvulsants with preserved sensorium.

He was a known case of alkaptonuria with ochronosis diagnosed at early forties and no other associated co-morbidities (hypertension, diabetes, smoking) and no other significant past medical, surgical or drug history.

On examination the patient was conscious, oriented. Pulse – 88 b/min, BP – 130/80 mmHg, fundus was normal, pupils were bilaterally equal and reactive to light, cranial nerves were normal, B/L upper limb and lower limb power was 5/5, b/l plantar was flexor.

Investigations

MRI Brain Plain and Contrast with Total Spine Screening

Multiple variable sized ring enhancing T1hypointense, T2/FLAIR hyperintense lesions are noted in right fronto-temporal region and insular cortex with marked perilesional FLAIR hyperintense signal and restricted diffusion, largest measuring 10×6×10.4mm in the temporal region, It also shows ill-defined post contrast enhancement. Associated abnormal leptomeningeal enhancement predominantly along right sided sylvian fissure and sulcal spaces of right fronto-temporal region with their effacement.

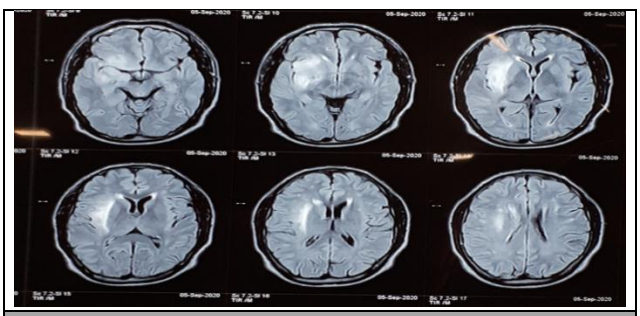

Figure 2. MRI Brain

All the visualized vertebrae show diffuse T2/STIR heterogenicity with fatty replacement of marrow s/o osteoporosis.

Spondylotic changes in the form of osteophytes seen in whole spine with disc desiccation and marginal osteophytes and reduced disc height at multiple levels: C4-5, C5-6, D2-3, D5, D5-6, D7-8, D11-12, D12-L1 and L4-5 with heterogenous signal in the disc spaces and end plates which reveal calcification on limited CT section -suggestive of ochronosis.

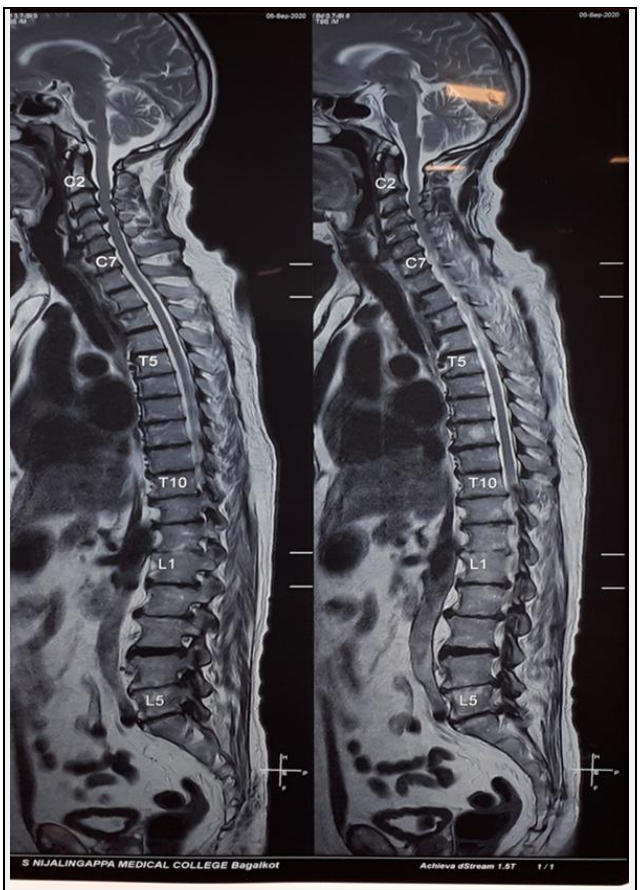

Figure 3. MRI Brain with whole spine screen

Altered signal intensity lesion involving right insula and temporal lobe showing mild diffusion restriction, patchy contrast enhancement, and necrosis. Elevated choline peak, rCBV, perilesional oedema and mild mass effect -likely neoplastic lesion (glioma).

Neurosurgery opinion advised for tissue biopsy. During tissue biopsy 70% of tumour excision was done and sent for histopathology reporting.

Histopathology Report of Biopsy Brain Tissue

Section study shows neuroparenchyma with an infiltrating, high grade glial neoplasm. Composed of fibrillary and protoplasmic astrocytes set in a fibrillary microcystic stroma. The individual tumour cells exhibit round to oval nuclei and moderate indistinct eosinophilic cytoplasm. A few bizarre cells with hyperchromatic nuclei are seen. Mitotic activity is increased. Microvascular proliferation and palisading necrosis are noted.

Final Impression

Glioblastoma, IDH wild type, WHO grade-IV; right temporal lobe.

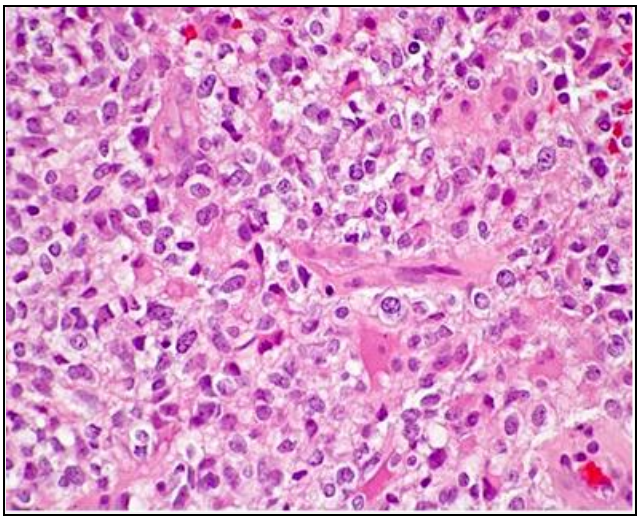

Figure 4. Glioblastoma, IDH Wild type with Oligodendroglioma Component. Uniform Round Nuclei with Perinuclear Halos (200X)

Patient underwent radiotherapy and chemotherapy, symptomatically improved and doing well.

Blood reports – Hb – 13.0g/dl, WBC–5,700/cu mm, Platelet 4,27,000/cu mm, PT/INR, S. Urea, S. Creatinine, S. Electrolytes, Urine routine, lipid profile and LFT were Normal.

CSF analysis and CRP were done and within normal limits, Mantoux test RA factor was negative.

DISCUSSION

Alkaptonuria is a complicating inflammatory multisystemic disease, in which anybody distinctly expressing HGD may be affected.[3] Although major AKU pathological features (i.e., ochronotic arthropathy, renal, and cardiovascular complications) are clinically well described, the neurological implications of the pathology are still totally neglected[2]. Several lines of evidence suggest a possible association between AKU and Parkinson's disease.[3] As far as central nervous system, ochronosis has been found in the brain of AKU patients.[3] In another AKU case, extensive ochronotic pigment deposition was found in dura mater as well as in the walls of the dural sinuses.[3] Pigmented areas were also found in pineal gland and pituitary body. On the other hand, neurological manifestations in AKU patients have also been described, like cases of astrocytoma and concomitant pituitary adenoma, neuroblastoma, migraine headaches, and depression.[3] Particularly, the association of AKU and Parkinson disease (PD) has been reported, probably due to ochronotic pigment deposition.[3]

AKU patients suffer from cardiovascular disease and kidney disease, but may also have other organ severe implications, and may be complicated by secondary amyloidosis.[3] HGD has been expressed in liver, kidney, prostate, small intestine, colon. More recently, we also reported that the osteoarticular compartment cells express HGD and thus contribute to the production of local ochronosis in AKU arthropathy.[3]

Glioblastoma multiforme develops mainly in the brain. This neoplasm is located in hemispheres or subtentorially in the brain stem and cerebellum.[1] It is characterized by infiltrating growth; therefore, the tumour mass is not clearly distinguishable from the normal tissue, a growing tumour causes an increase of intracranial pressure, and sometimes it leads to hydrocephaly.[1] Metastases of this neoplasm by cerebrospinal fluid or blood are rare and target the spleen, pleura, lungs, lymph nodes, liver, bones, pancreas and small intestine[1]. It has been hypothesized that the low metastatic potential of GBM results from the barrier created by cerebral meninges, but also from the rapid tumour growth and short course of this disease.[1] The brain is devoid of lymphatic vessels, so metastases through this pathway is impossible.[1]

DISCUSSION OF MANAGEMENT

There is no effective cure for AKU at the moment[2]. Treatment is symptomatic while for the end-stage, total joint replacement is required.[3] Phase II and a phase III clinical trials with nitisinone, the only orphan drug so far recognized for AKU, is currently active.[3]

Glioblastoma multiforme is characterized by high proliferative activity.[1] Since GBM infiltrates surrounding tissues, its complete resection is impossible and radiotherapy not always efficient.[1] The blood-brain barrier makes treatment more difficult and tumour cells found in the areas of hypoxia are resistant to radiotherapy.[1] Anti-cancer treatment should lead to tumour regression and provides as long as possible disease-free survival.[1] Surgical resection to the extent feasible, followed by chemotherapy and radiotherapy, is the mainstay of GBM treatment.[1] Surgical treatment, chemotherapy and radiotherapy prolong the survival time in young people up to 202 weeks.[1] The best results are obtained when radiotherapy is performed after the surgery, with the doses of 5000–6000 cGy. Dose escalation over 6000 cGy has resulted in increased toxicity without a survival benefit.[1]

The standard treatment scheme for glioma most frequently includes temozolomide.[1] When comparing the results of chemotherapy, the highest median survival time is observed in patients treated with temozolomide, in comparison to another chemotherapeutics.[1] It is known that the survival advantage among patients treated with temozolomide, and radiotherapy is longer compared to radiotherapy alone[1]. The addition of temozolomide to radiotherapy for newly diagnosed glioblastoma is connected with minimal additional toxicity.[1] Despite optimal therapy, glioblastomas invariably recur. Treatment options for recurrent disease may include reoperation, carmustine wafers, and alternate chemotherapeutic regimens.[5]

FINAL DIAGNOSIS

Glioblastoma multiforme secondary to alkaptonuria.

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Disclosure forms provided by the authors are available with the full text of this article at jemds.com.

REFERENCES

[1] Urbanska K, Sokotowska J, Szmidt M, et al. Glioblastoma multiforme - an overview. Contemp Oncol 2014;18(5):307-12.

[2] Murray RK, Granner DK, Mayes PA, et al, eds. Harper's illustrated biochemistry. 26th edn. Lange Medical Books/McGraw-Hill Education 2003:254-5.

[3] Bernardini G, Laschi M, Geminiani M, et al. Homogentisate 1,2 dioxygenase is expressed in brain: implication in alkaptonuria. J Inherit Metab Dis 2015;38(5):807-14.

[4] Millucci L, Ghezzi1 L, Bernardini G, et al. Diagnosis of secondary amyloidosis in alkaptonuria. Diagn Pathol 2014;9:185.

[5] Jamesen LJ, Kasper LL, Lonogo DL, et al, eds. Harrison's Principles of internal medicine. 20th edn. Vol. 2. The McGraw-Hill Companies 2019:645-46.