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Sorafenib induced optic neuropathy

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Abstract

Sorafenib is a protein kinase inhibitor, a drug approved for primary renal cell
cancer,radioactive iodine resistant advanced thyroid carcinoma,unresectable hepatocellular carcinoma.It is an inhibitor of Raf kinase,VEGF receptor 2 and 3, platelet derived growth factor (PDGF) and c kit, the receptor of stem cell factor.Sorafenib undergo oxidative metabolism with a half life of 25-48hours and is metabolised by liver.Common adverse
effects of sorafenib include dermatological events like rash, palmar-plantar erythrodysesthesia.Others include diarrhoea, fatigue,headache ,abdominal pain,nausea.Periodic blood tests to monitor complete blood counts as well as function of organs like kidney and liver are advised.Our aim is to present a patient of sixteen years of age, a known case retroperitoneal fibromatosis,post surgical resection on sorafenib with previous normal vision proceeded to diminution of vision in both eyes associated with fundus changes suggesting demyelinating optic neuropathy highlighting the importance of baseline ocular examination before starting a chemotherapeutic agent like sorafenib and
periodic follow up for visual complaints after initiating the treatment .

Keyword: Sorafenib,optic neuropathy,Retroperitoneal fibromatosis,drug toxicity

Introduction

Sorafenib is a targeted cancer drug also known by its brand name ,Nexavar approved by US FDA(United Stated Food and Drug Administration) as the first line therapy for advanced cancer of liver, kidney and thyroid(Gong *et al.,* 2017 and Behbehani, 2007)[1], [2].It was found that sorafenib block proliferation of cells and new vessel formation leading to prolongation of the overall survival(L. Liu *et al.,* 2006)[3].Despite of this benefit, side effects have been reported which varied from patient to patient depending upon the drug kinetic like bioavailability of the drug.

Retroperitoneal fibromatosis is a group of mesenchymal tumors with monoclonal proliferation of fibroblasts and myofibroblasts with inter cellular collagen production which also can infiltrate muscles and deeper structures(Campara *et al.*,2016)[4].Diagnosis is made on clinical presentation , radiological and histological features.In a retrospective analysis ,a response rate of 25% was seen with a starting oral dose of 400mg once a day with Sorafenib

as evaluated with Response Evaluation Criteria In Solid Tumors (RECIST),version 1.1(M. M. Gounder *et al.*, 2018)[5]. Sorafenib has an acceptable safety and has improved the quality of life according to the literature.The fact that RECIST may underestimate the efficacy was pinpointed in the above mentioned retrospective study,and a magnetic resonance imaging (MRI)T2-weighted signal intensity may be a better imaging bio marker to signify a biological transformation to a collagenous scar from a cellular tumor(M. M. Gounder *et al.*, 2011)[6].Such an imaging modality is required to study the shift to a collagenous scar from a cellular mass to assess the treatment effects of Sorafenib on retroperitoneal fibromatosis(W. D. Tap *et al.*, 2015)[7].The appropriate duration of treatment with Sorafenib,its benefit and its cost relative to the existing therapies is not known(M. Sundaram *et al.*,1987)[8].In desmoid tumor the mechanism of action of the chemotherapeutic drug Sorafenib remains unknown.Investigations screening gene expression and protein phosphorylation of receptor tyrosine kinases like fibroblast growth factor receptor, platelet derived growth factor receptor and transforming growth factor beta receptor and the Wnt signaling pathway are ongoing(M. M. Gounder *et al.*, 2018)[5].

Case presentation

We are presenting a sixteen year old female a known case of retroperitoneal fibromatosis,post surgical excision with histopathology showing desmoid fibromatosis was started on Sorafenib following which she developed rashes.Hence the medicine was discontinued and was restarted one month later.Four months following this patient presented with alopecia,decreased sensation in both feet with diminution of vision in both eyes.On examination unaided visual acuity had decreased from 6/6, N6 to counting fingers at 2meter,N8 in both eyes in a span of 2 months.Both eyes pupils were 3mm in size,sluggishly reactive with no relative afferent pupillary defect(RAPD).Lens was clear,extra ocular movements were full and free in both eyes and fundus (Figure 1)showed bilateral temporal pallor of disc.Neurological and other systemic examination was unremarkable.MRI Brain (Figure 2) showed demyelination changes in right thalamo capsular region,MRI Orbit was normal.On lumbar puncture CSF analysis showed mildly elevated proteins, negative NMO antibody,negative antibody titre for MOG and no oligoclonal bands.

Humphrey's visual fields (Figure 3)showed bilateral central scotoma and visual evoked potential (VEP) showed increased latency in right side suggestive of right anterior visual pathway conduction defect.

Neurology opinion was sought and the patient was diagnosed with Sorafenib induced bilateral demyelinating optic neuropathy.Patient was treated with intravenous methylprednisolone for three days and was started on tapering oral steroids.Sorafenib was discontinued immediately.Ten days following the discontinuation of Sorafenib, patient's best corrected visual acuity improved to 6/6, N6 and restoration of color vision to 24 out of 24 plates.Fundus examination showed marked reduction in optic disc pallor in both the eyes

Discussion

Optic neuropathies can be defined as disorders involving degeneration of the optic nerve.Presenting symptoms include progressive and painless diminution of vision typically bilateral with optic disc pallor, dyschromatopsia and visual field defects(R. P, R. V, and A. J,2018 and P. Sharma and R. Sharma,2011)[9], [10].In drug induced optic neuropathy, withdrawal of the causative drug can lead to reversal of symptoms,if detected early(R. P, R. V, and A. J,2018 andM. J. Lloyd and F. W. Fraunfelder 2007)[9], [11].Other common adverse effects of Sorafenib include hand foot skin reaction,diarrhoea, hypertension and fatigue.However cardiovascular events can lead to death(Y. Li, Z.-H. Gao, and X.-J. Qu,2015)[12].Most common drugs causing drug induced optic neuropathy include ethambutol, alcohol,amiodarone,immunosuppressants like methotrexate and cyclosporine(Behbehani, 2007)[2].Potential risk of such drugs should be addressed to the patient before initiating the therapy.

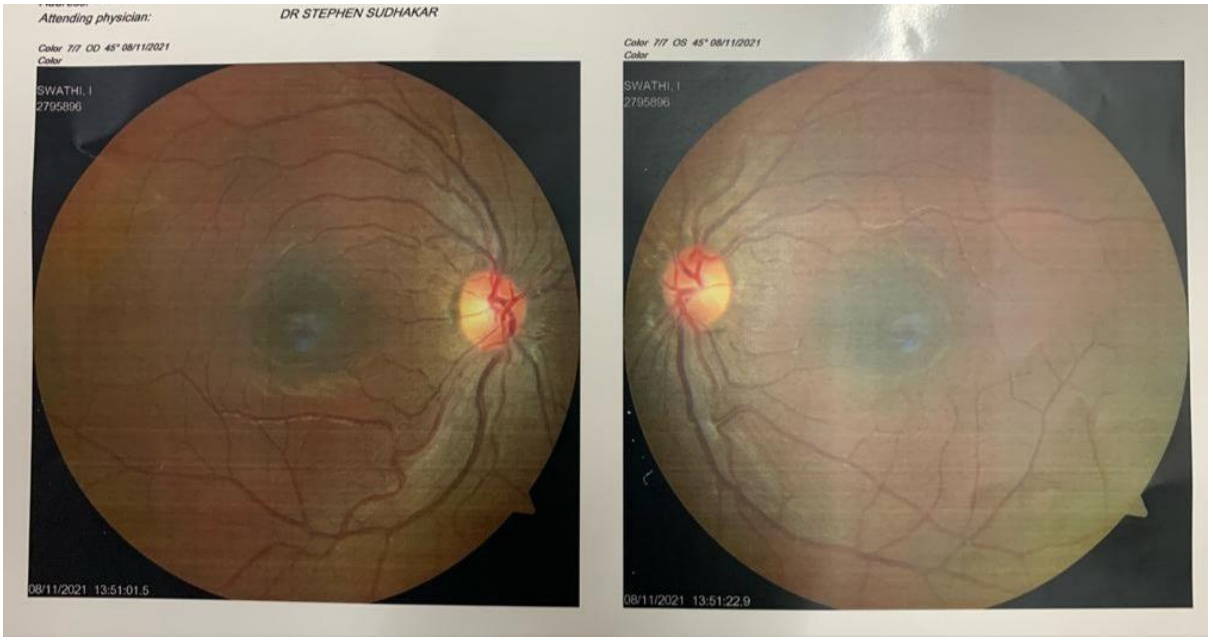


Figure 1: Fundus photo both eyes showing temporal pallor of the optic disc

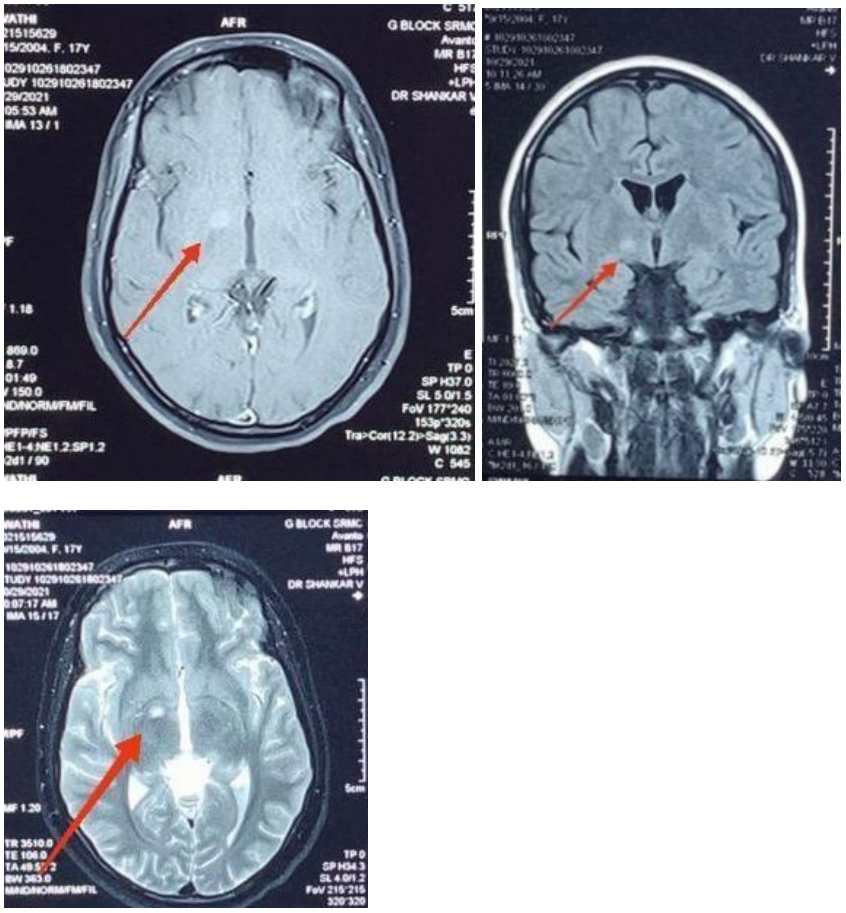
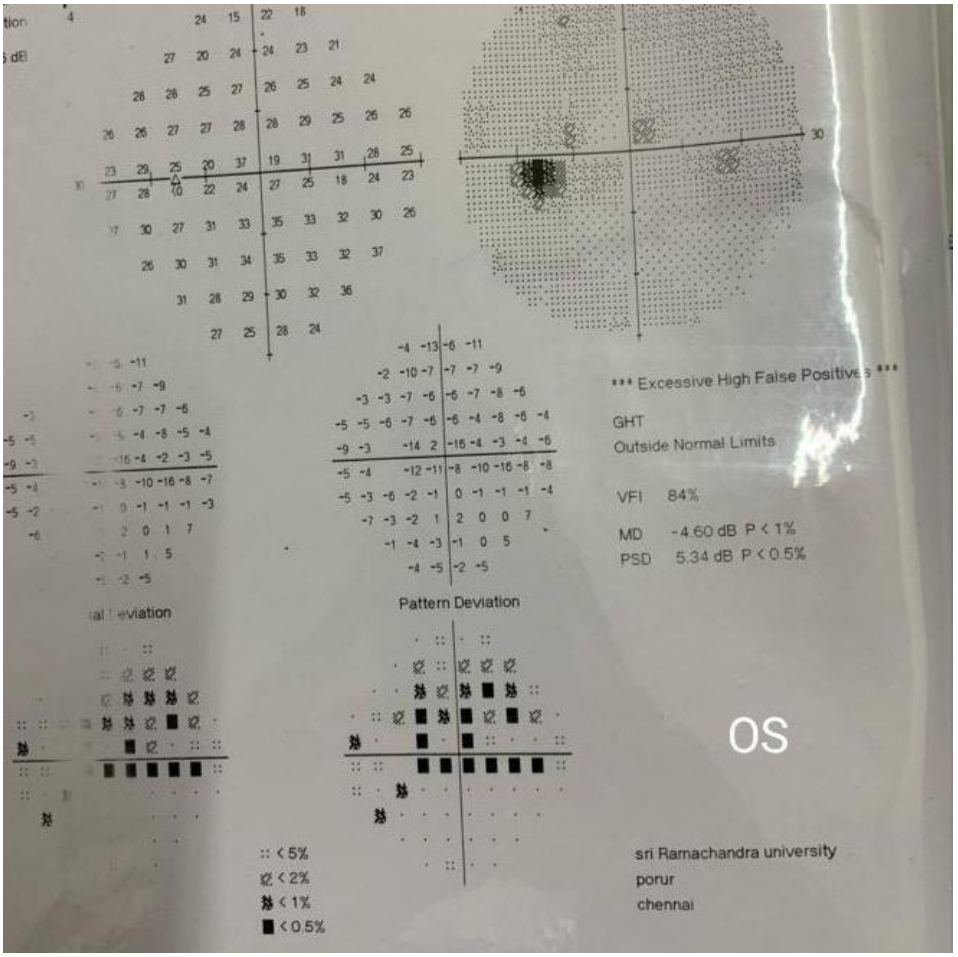


Figure 2:MRI Brain showed demyelination changes in right thalamo capsular region


*** Excessive High False Positives ***
GHT
Outside Normal Limits
VFI 84%
MD -4.60 dB P < 1%
PSD 5.34 dB P < 0.5%
Pattern Deviation
OS
:: < 5%
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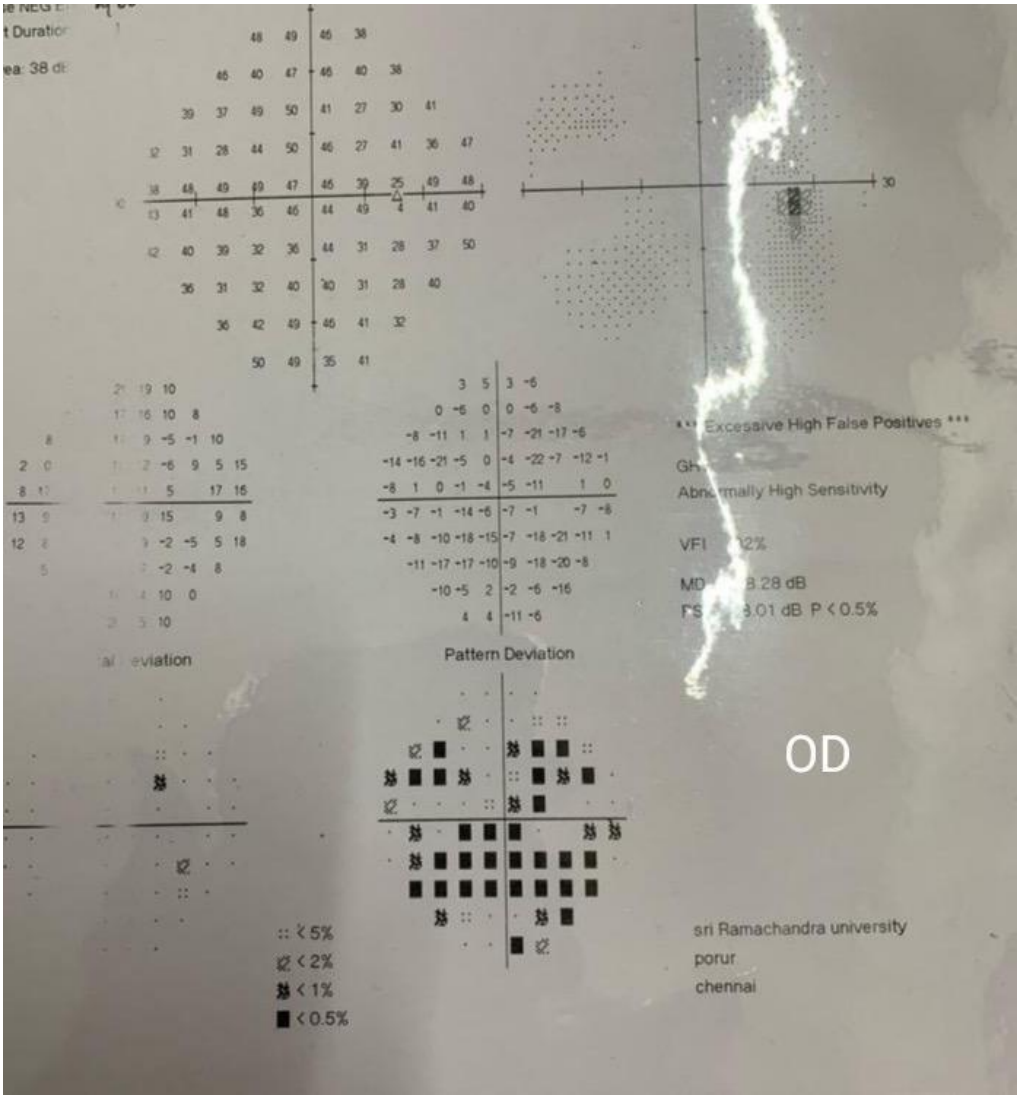

Figure 3:Humphrey's visual fields showing bilateral central scotoma

Conclusion

We conclude that Sorafenib was found to cause demyelinating optic neuropathy as prompt withdrawal of the drug lead to the relief of symptoms.Base line ophthalmology evaluation in every patient planning to start on Sorafenib and follow up regularly for ocular symptoms and signs once on treatment is advisable.

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