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Zoledronic Acid Induced Orbital Cellulitis-Case Report & Literature Review.

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Abstract*: Bisphosphonates; synthetic analogues of intrinsic bone mineralization regulator pyrophosphate has revolutionized the management of post menopausal osteoporosis and have found a wide gamut of applications in the management of metabolic and metastatic bone disease. We report the case of a 54 year old lady, diagnosed case of metastatic carcinoma breast who developed acute onset orbital cellulitis within 24 hours of infusion of zoledronic acid. The patient was managed conservatively with high dose prednisolone for 5 days and tapered over 3 weeks, with complete resolution of orbital signs & symptoms within 2 weeks of the event with no residual stigmata. These orphan but dramatic events like non-infective orbital cellulitis are extremely rare with <20 cases reported in medical literature. Bisphosphonates are generally safe and tolerated well and as the use and clinical data expands, side effects albeit isolated are being documented in trials and surveillance.*
Key-words*: Bisphosphonates, Zoledronic acid.*

I. Introduction

Bisphosphonates are synthetic analogues of endogenous bone matrix mineralization regulator "pyrophosphate" and act by improving mineral density, suppression of bone turn over and reduction of fracture risk, and have found a wide gamut of uses including management of post menopausal osteoporosis, hypercalcaemia of malignancy, Pagets disease, multiple myeloma, bony metastases from systemic malignancies and also under evaluation for use in steroid induced osteoporosis, male osteoporosis, osteoporosis in hormone suppression therapy, osteoporosis in transplant recipients, and HIV related bone loss.

II. Case Report

54 year old lady diagnosed with right breast infiltrating duct carcinoma, underwent modified radical mastectomy and histopathology revealed Infiltrating duct carcinoma grade II-III, ER+PR+ Her-2 neu-Negative.

Patient received 4 cycles of chemotherapy consisting of adriamycin and cyclophosphamide followed by 4 cycles of docetaxel from April 2013 to October 2013, and then was referred for radiation (50 Gy in 25 fractions over 36 days).The patient was then started on tamoxifene 20 mg/day from November 2013.

The period from November 2013 to October 2014 was uneventful, then in November 2014 patient started experiencing vague aches in lower back and hips and patient was referred for FDG-PET CT scan which revealed multiple metabolically active sclerotic lesions in the head of left humerus, body of $D_{8,}$ D_{9}, $D_{12,}$ L1 vertebrae and the right iliac bone .Patient was started on letrozole 2.5 mg/day and zoledronic acid 4 mg once a month, in view of osseous metastases.

Within 24 hours of administration of first dose of zoledronic acid patient developed pain and lacrimation in the right eye, along with ptosis, swelling of eyelid, restriction of eye movements and diminution of vision. Hertels exopthalmometer revealed 2.5 mm of proptosis and slit lamp examination revealed marked conjunctival hyperaemia and chemosis along with markedly swollen and tender periorbital tissue. The pupils were reacting normally to light with no afferent pupillary defect and posterior chamber examination was normal.

Contrast enhanced MRI of brain and orbits revealed ill defined enhancing soft tissue swelling in preseptal region of right orbit along with soft tissue stranding of the anterior retrobulbar fat involving the intra as well as the extraconal compartments, also minimal edematous changes seen in the wall of right globe with abnormal post contrast enhancement. Extraocular muscles of right side were mildly edematous, minimal enhancement of anterior right optic nerve sheath with a normal optic nerve. Left orbits and its contents, brain parenchyma, ventricular system and cavernous sinuses were normal.

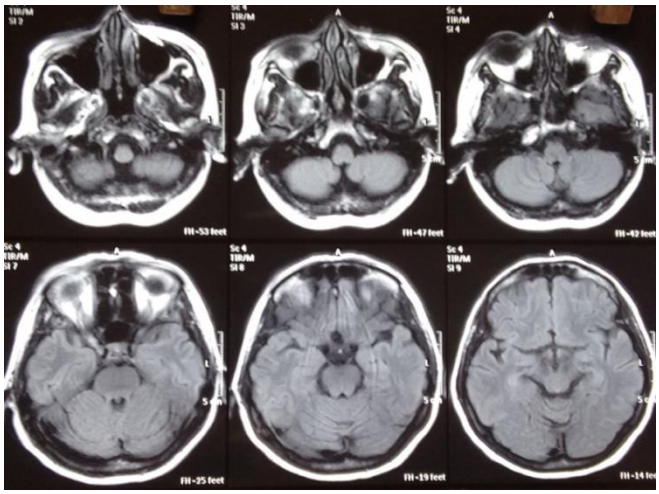

Fig.1: MRI; axial plane-shows diffuse soft tissue enhancement and stranding of retrobulbar fat with post contrast enhancement of the right orbit.

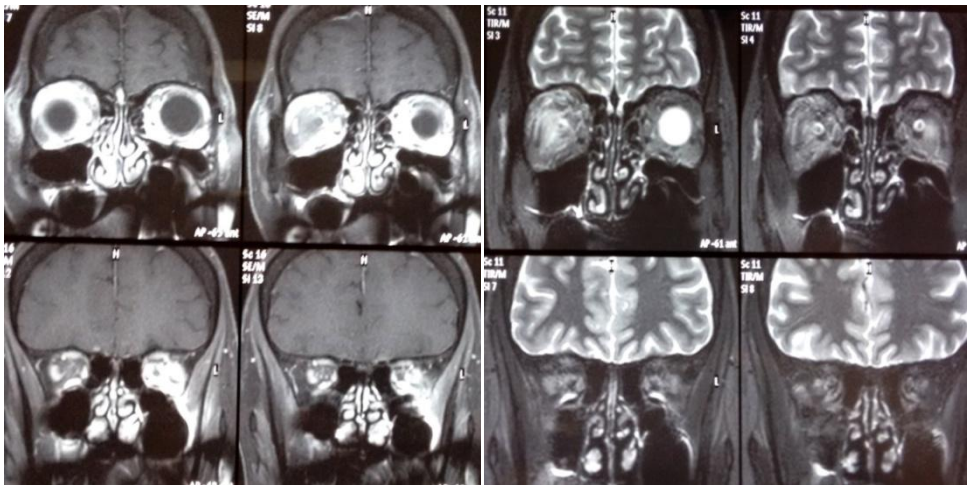

Fig.2 & 3: MRI; coronal plane- reveals diffuse ill defined heterogeneous soft tissue enhancement & fat stranding of right orbit.

So a diagnosis of zoledronic acid induced orbital cellulitis was reached, and patient was put on Prednisolone 1 gm/day x 5 days along with topical steroid and antibiotic eye drops.

The patient responded well with good subjective improvement within 48 hours of starting steroids, the steroids were tapered over 3 weeks, and on follow up in the oncology out patient department of Saifee hospital after 3 weeks revealed complete resolution of the orbital signs and symptoms.

The patient was rechallenged with zoledronic acid about 6 weeks from the event, but no untoward reaction was elicited, accordingly patient is on monthly zoledronic acid.

III. Discussion

Bisphosphonates are synthetic analogues of endogenous bone matrix mineralization regulator "Pyrophosphate" with a wide spectrum of uses in post menopausal osteoporosis, hypercalcaemia of malignancy, bone metastases from systemic malignancies, multiple myeloma, Pagets disease, and is also under evaluation for use in male osteoporosis, steroid induced osteoporosis, osteoporosis in hormone suppression therapy, osteoporosis in transplant recipients, and HIV related bone loss. [1, 2]

They are associated with improvement of bone mineral density, suppression of osseous turnover and a real time reduction of fracture risk and morbidity.

3.1. Pharmacology Of Bisphosphonates. [1, 2, 3]

Bisphosphonates are composed of an enzyme resistant Phosphorus-Carbon-Phosphorus (P-C-P) skeleton which acts as the ''bone hook'', and R1 and R2 side chain moieties. The P-C-P nucleus and R1 side chain anchor binds hydroxyapatite crystals in the bone, while R2 moiety exerts biological activity owing to the presence of nitrogen atom.

3.2. Pharmacokinetics And Pharmacodynamics Of Bisphosphonates. [2, 3, 4]

Bisphosphonates have very poor oral absorption (<1%) but 100% bioavailability when administered intravenously, they bind to plasma proteins and are excreted unchanged via kidneys. They have no hepatic or cytochrome P450 metabolism, also no known active metabolites or drug interactions.

3.3. Mechanism Of Action Of Bisphosphonates. [2, 3, 4]

Bisphosphonates are classified as "Nitrogen containing" and "Non-Nitrogen containing bisphosphonates," nitrogen containing bisphosphonates, which includes the likes of pamidronate, zoledronate, alendronate, risedronate are among the more potent and longer acting formulations.

Bisphosphonates act by hindering protein prenylation by inhibition of farnesyl pyrophosphate synthase (FFP) of mevalonate pathway, thus preventing the post-translational prenylation of GTP-binding regulatory proteins like Ras, Rho etc, which regulate osteoclast morphology, differentiation, cytoskeletal rearrangement, function, membrane ruffling and trafficking thus leading to an attenuated resorptive function and accelerated apoptosis. Also mounting evidence suggests that osteoblastic proliferation, differentiation, maturation and function are upregulated and so is osteoblastic production of extracellular matrix, proteins, & growth factors.

Also upregulation of β-FGF, BMP-2, bone sialoproteins, OPG/RANKL system increases the overall tensile strength of bone.

3.4. Zoledronic Acid. [2]

A newer potent nitrogen containing bisphosphonate with the highest bone affinity and action owing to a unique chemical structure where the R2 moiety is composed of a heterocyclic ring containing 2-nitrogen atoms, it is given as an intravenous infusion over 15-20 minutes, with 100% bioavailability with bone concentrations >100x that of plasma concentrations, with reduction of bone turnover marker of >80% at 1 month post-infusion and a prolonged duration of action of over 6-8 months.

3.5. Complications

Complications associated with bisphosphonate use are rare and occurring in <2% of the patients, with the complications being generally mild, rarely warranting discontinuation of therapy.

1. Ocular Complications-

Ocular complications are following an intravenous infusion of zoledronic acid is rare with an estimated incidence of 0.05%,[5] and the complications range from eye pain & lacrimation to more severe manifestations which include conjunctivitis, scleritis, episcleritis, uveitis, orbital inflammation, optic nerve inflammation and cranial nerve palsies.

Ocular complications typically occur within 6-48 hours of infusion of the first dose to 6 days thereafter, with non-specific conjunctivitis being the most common ocular side effect of bisphosphonate use and uveitis being the least common.[2] Opthalmological symptoms in order of frequency include unilateral eye pain (89%), diplopia (50%), and blurry vision (33%), & signs include, lid edema (94%), conjunctival hyperaemia (83%), conjunctival chemosis (78%), motility defect (61%), proptosis (50%), anterior uveitis (22%), fundal abnormalities & afferent papillary defects (17%). Ocular symptoms are commonly preceded by systemic symptoms which include fever, malaise, bodyache. [6, 7]

Reid et al. in their detailed analyses of the adverse events associated with use of IV zoledronic acid vs. placebo in the management of post menopausal osteoporosis reported a 42% acute phase reaction rate vs. 11% in the placebo group, with 90% of the acute phase reactions being rated as mild to moderate. [8]

French DD et al. in their cohort based prospective study, documented the relative incidence of uveitis and scleritis as 1.23 in the treatment arm group vs. placebo over a period of 6 months. [9]

Studies have shown association between preexisting autoimmune disorders like ankylosing spondylitis, Behcets syndrome, SLE, Wegeners granulomatosis, and also drugs such as rifabutin, cidofovir, TMP-SMX, where in bisphosphonates might just act as triggers to an inflammatory cascade.[2,6]

Amino bisphosphonates like pamidronate, zolendronate share several epitopes homologous with non peptide γ/δ –T-cell ligands that induce lymphocyte activation and release reaction. [2, 6]

It is speculated that orbital cellulitis represents an exaggerated APR phenomenon, with prompt response to systemic glucocorticoids with a benign course and no residual stigmata. [6]

2. Acute Phase Reaction-

Amongst the most common complications of bisphosphonate administration, and presenting with fever, myalgia, arthalgia, headache, with symptoms starting within hours of administration, and by rule self limited.

Black DM et al. in his study of uses of zoledronic acid in post menopausal osteoporosis reported pyrexia (16.1%), myalgia (9.5%), flu like symptoms (7.8%), headache (7.1%), and artharlgia (6.3%).Also the incidence and severity decreased with each subsequent infusion i.e. 30% after 1st infusion, 6.6% after 2nd and 2.8% after the 3rd dose .[10]

Saad F et al. in his study of role of zoledronic acid in hormone refractory prostate cancer with bone metastases, reported the incidence of myalgia(25%), fever(21%) vs. 18% and 13% in the placebo control group.[11]

These acute phase reactions are quite common and are due to the direct activation of γ/δ lymphocytes with intracellular accumulation of isopentenyl pyrophosphate due to inhibition of farnesyl diphosphate synthase of cholesterol pathway. [12]

3. Gastrointestinal Intolerance-

Upper gastrointestinal complaints are particularly common with the use of oral bisphosphonates like pamidronate and common afflictions being nausea, vomiting, epigastric discomfort and dyspepsia.

Esophagitis is a common complication and is related to the use of oral bisphosphonates, which now have been mitigated by the use of parenteral preparations. [1, 2]

4. Renal Complications-

Bisphosphonates are excreted exclusively by the kidneys with and are associated with both acute and chronic kidney injury and nephrotic syndrome. Zoledronate has been implicated in most cases of renal failure(acute tubular necrosis), pamidronate in nephrotic syndrome (Collapsing focal segmental glomerulosclerosis) and ibandronate appears to be the least nephrotoxic. [1, 2]

Risk of nephrotoxicity is directly related to the drug dosage, infusion time, age, preexisting renal disease, hypercalcemia, and concomitant use of nephrotoxic drugs like NSAIDS. [1]

In the HORIZON pivotal fracture trial which evaluated the safety profile of zoledronic acid, found no significant renal impairment following 3 years of IV zoledronic infusion in patients with baseline creatinine clearance>30 ml/min.[2, 10]

Boonen S et al. in their study of management of post menopausal osteoporosis, in 31 patients treated with zoledronic acid, transient elevation of creatinine levels had been observed, which normalized completely within 1 month in 27 patients and in all by end of 1 year, and follow up assessment at 12, 24, and 36 months showed no significant changes in serum creatinine or creatinine clearance from baseline. [13]

Most of the renal complications can be avoided by increasing the infusion time to >15 minutes and post infusion hydration, caution is warranted in use in patients with creatinine clearance <30 ml/min or creatinine >3 mg/dl. [1, 14, 15]

5. Osteonecrosis Of Mandible And Maxilla-

Osteonecrosis of jaw is a rare but oft mentioned complication of bisphosphonate therapy, a form of chronic osteomyelitis involving the maxilla or mandible.

The most common site being the posterior aspect of mandible in the region of mylohyoid ridge, and the organisms commonly isolated include Actinomyces israelii and normal oral mucosal flora. [16]

Dental procedure is the most common precipitating factor, and the predisposing factors include long term bisphosphonate therapy, metastatic solid tumors, multiple myeloma, poor dental health, coexisting morbidities like DM, or high dose steroid therapy. Cumulative bisphosphonate dose has been suggested to be the most important risk factor for the development of osteonecrosis of jaw. [16, 17]

In the HORIZON study group, no cases of osteonecrosis of jaw were reported in the 7000 study subjects, and retrospective analysis revealed 1 case each in the control and placebo group. [19]

Treatment includes discontinuation of bisphosphonates, systemic antibiotics, chlorhexidine mouth wash, and minor wound debridement. Rarely have patients required more aggressive management like sequestrectomy, mandibular or maxillary resection. [17, 18, 20]

6. Atypical Femoral Diaphyseal Fractures-

Long term alendronate use has been associated with low energy proximal femoral diaphyseal fractures, radiological features are typical and defined as a transverse or oblique fracture with breaking of the cortex and diffuse cortical thickening of proximal femoral shaft. [21, 22]

Most fractures involve the proximal femoral diaphysis or subtrochanteric region. Bone biopsies have revealed severely suppressed osseous turnover which may be the underlying pathology to this adynamic bone disease. [21, 22, 23]

Patients on long term bisphosphonate therapy must be cautioned about persistent pain in the upper part hip, which may herald an impending pathological fracture.

7. **Electrolyte Imbalance**-

Bisphosphonates esp.zoledronic acid is associated with transient hypocalcaemia and hypophosphataemia, along with a secondary parathormone increase. Risk factors for hypocalcemia include vitamin D deficiency, hypoparathyroidism , chronic renal disease, and concomitant hypomagnesaemia.[1, 2]

In the HORIZON-PFT trial, 2.3% of the patients in the zoledronic acid group showed hypocalcemia; defined as serum calcium < 2.075 mmol/L, 9-11 days after the first infusion and all cases were transient and asymptomatic, other electrolyte abnormalities include hypophosphataemia, and hypomagnesaemia. [2, 10]

Preventive measures include appropriate calcium and vitamin D supplementation.

IV. Conclusion

Bisphosphonates especially zoledronic acid are novel drugs that have revolutionized the management of osteoporosis and malignancy associated bone disease, as our understanding about these novel agents increase, so does their complications and associated side effects come to the fore. A discerning eye and prompt management is the cornerstone of management of most complications.

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