Journal of Clinical Orthopaedics and Trauma 9S (2018) S26–S28

Contents lists available at ScienceDirect

Journal of Clinical Orthopaedics and Trauma

journal homepage: www.elsevier.com/locate/jcot

Case report

Nilotinib induced avascular necrosis of femoral head in an adult chronic myeloid leukemia patient

Shinto Francis Thekkudan, Soniya Nityanand*

Department of Hematology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, 226014, Uttar Pradesh, India

ARTICLE INFO

Article history:
Received 25 August 2017
Received in revised form 21 November 2017
Accepted 23 November 2017
Available online 24 November 2017

Keywords:
Nilotinib
Tyrosine kinase inhibitor
Avascular necrosis of femoral head
Chronic myeloid leukemia

ABSTRACT

We report a rare case of avascular necrosis of femoral head (AVNFH) in an adult chronic myeloid leukemia – chronic phase (CML-CP) patient during due course of therapy with second line Tyrosine Kinase Inhibitor (TKI), Nilotinib. A high index of clinical suspicion should be kept in any symptomatic CML patient on TKI's.

1. Introduction

Nilotinib is a tyrosine kinase inhibitor approved for the treatment of adult patients with newly diagnosed CML-CP and for patients with Imatinib-resistant or Imatinib-intolerant CML-CP or accelerated phase (AP). AVNFH occurs due to traumatic as well as non-traumatic causes. AVNFH has been rarely reported in CML with only few case reports available in the literature.[1–6] AVNFH developing during TKI therapy is even more rare; there are only 2 cases reported – one each with Imatinib[7] and Dasatinib,[8] respectively. We report the first case of Nilotinib causing AVNFH in a CML-CP patient, along with a literature review of incidence of AVNFH in CML.

2. Case report

A 47-year-old male diagnosed as CML in chronic phase in 2008, was initially started on Imatinib 400 mg/day, which was later increased to 600 mg/day. Since Feb 2015 due to a progressive rise of BCR ABL transcript ratio, Imatinib resistance mutational analysis was done which revealed direct binding site F317L kinase domain mutation. He was thus switched to Nilotinib. After 9 months of Nilotinib therapy, he presented with 15 days history of dull aching pain in left side of hip with radiation along the medial aspect of left thigh. There was no history of fall or trauma. Clinical examination was unremarkable. Hemogram & peripheral smear were normal and suggestive of complete hematological remission. He had a negative ANA and sickling test. His lipid profile also was normal. BCR- ABL transcript ratio was 16% by qPCR (IS). Radiological evaluation by X-ray hip was suggestive of AVNFH in the left side (Fig. 1A), which was further confirmed by contrast Magnetic Resonance Imaging (Fig. 1B–D). He is presently planned for a total hip replacement.

3. Discussion

Incidence of AVNFH in CML is not known because of the very few reports and absence of prospective studies addressing this issue. AVNFH has been described at the time of presentation as well as during Interferon (INF) α therapy in CML. 6 cases of AVNFH has been reported at the time of presentation (Table 1)[1–5] and 4 cases during the course of interferon therapy,[6] in CML. The mechanism proposed was due to leukocytosis and/or thrombocytosis causing microcirculatory occlusion or synergistic interaction between CML and INF α therapy leading to inhibition of angiogenesis. Interestingly there are no reports of AVNFH with INF α therapy for other indications.[6,9] In the TKI era, Nataraj et al. have reported a pediatric case of AVNFH associated with Imatinib in 2014.[7] Similarly a single case report of Dasatinib associated AVNFH was reported by Yassin et al. in 2015,[8] with authors concluding that the

Abbreviations: CML, Chronic myeloid leukemia; CP, Chronic phase; AP, Accelerated phase; AVNFH, Avascular necrosis of femoral head; ANA, Anti nuclear antibody; qPCR, Quantitative polymerase chain reaction; IS, International scale; TKI, Tyrosine kinase inhibitor; CHR, Complete hematological response; CCR, Complete cytological response; MMR, Major Molecular response.

* Corresponding author.

https://doi.org/10.1016/j.jcot.2017.11.015
0976-5662/

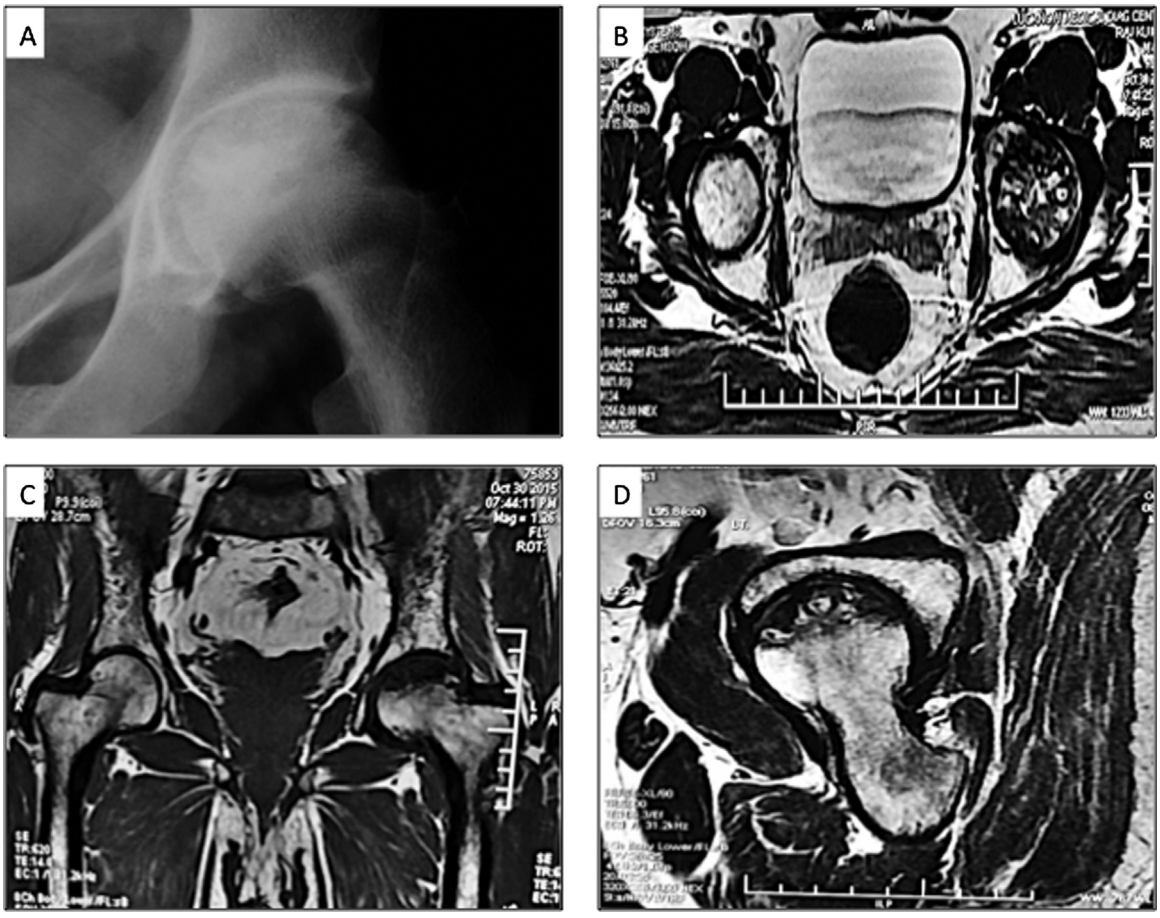

Fig 1. (A) Plain X Ray showing left femoral head with geographical appearance with mixed sclerotic and lucent areas, representing AVN related changes (**B**) MRI T1WI showing irregular articular surface of left femoral head with marked flattening and deformation. Left femoral head sub articular region shows 'crescent sign' (**C**) T2WI Left hip joint space is markedly reduced with sub articular sclerotic changes in acetabulum (**D**) T1WI showing signal intensity changes suggestive of edema, noted in acetabulum, head and neck of femur.

Table 1
Literature review of reported cases of AVNFH in CML cases.

CML presenting with AVNFH				
No.	Age/Sex	PARAMETERS	YEAR	REFERENCE
1	17/M	Unknown	1984	Gibson et al.[2]
2	9/F	TLC–359 × 109/L Plt- 809 × 109/L	1988	Salimi et al.[3]
3	17/M	Unknown	1996	Leone, et al.[4]
4	15/F	Hb-10.8 g/dL TLC–290 × 109/L Plt- 250 × 109/L	2003	Gupta et al.[1]
5	24/M	Hb-10.4 TLC-96.8 × 109/L Plt- 684 × 109/L	2005	Moon et al.[10]
6	12/F	Unknown	2014	Kumar et al.[5]

AVNFH on INF α therapy for CML				
No.	Age/Sex	PARAMETERS	Duration Of Rx with INF α (months)	REFERENCE
1	22/M	TLC – 2.5–3.5 × 109/L Plt – 61–140 × 109/L	18	Kozuch et al.[6]
2	45/F	TLC – 15 × 109/L Plt – 120–210 × 109/L	54	
3	46/F	TLC – 8.4–18 × 109/L Plt – 160–220 × 109/L	6	
4	17/M	TLC – 167 × 109/L Plt – 895 × 109/L	1	
5	25/F	TLC – 49 × 109/L Plt – 1200 × 109/L	48	

Table 1 (*Continued*)

AVNFH on TKI therapy				
No.	Age/Sex	PARAMETERS	Interval from diagnosis	REFERENCE
1	12/M	TLC – 5.6 × 109/L	8 years Imatinib × 8 years Dose escalated to 600 mg/day for 1 year	Nataraj et al.[7]
2	34/F	Hb – 13 g/dL TLC – 6 × 109/L Plt–235 × 109/dL	3 years Dasatinib x 18 months- (in CHR, CCR, MMR)	Yassin et al.[8]
3	47/M	Hb – 12.5 g/dL TLC – 5 × 109/L Plt – 335 × 109/dL	7 years Nilotinib x 9 months Not in MMR	Present case, 2017

scarcity of reports may be due to either the rarity of the condition or under reporting of cases.

4. Conclusion

To the best of our ability we could not find any cases of AVNFH reported with Nilotinib. Our patient did not have any other cause attributable. Further he had normal WBC and platelet counts and was in hematological remission at the time of presentation. So AVNFH should be thought of in any symptomatic CML patient on TKI's.

Conflict of interest

The authors have none to declare.

References

1. Gupta D, Gaiha M, Siddaraju N, Daga MK, Anuradha S. Chronic myeloid leukemia presenting with avascular necrosis of femur head. *J Assoc Physicians India*. 2003;51:214–215.
2. Gibson J, Joshua DE, Collis D, Kronenberg H. Chronic myeloid leukaemia presenting as femoral head necrosis. *Scand J Haematol*. 1984;32:376–378.
3. Salimi Z, Vas W, Sundaram M. Avascular bone necrosis in an untreated case of chronic myelogenous leukemia. *Skeletal Radiol*. 1988;17:353–355.
4. Leone J, Vilque JP, Pignon B, et al. Avascular necrosis of the femoral head as a complication of chronic myelogenous leukemia. *Skeletal Radiol*. 1996;25:696–698.
5. Kumar S, Bansal D, Prakash M, Sharma P. Avascular necrosis of femoral head as the initial manifestation of CML. *Pediatric Hematol Oncol*. 2014;31(6):568–573.
6. Kozuch P, Talpaz M, Faderl S, et al. Avascular necrosis of the femoral head in chronic myeloid leukaemia patients treated with interferon-alpha: a synergistic correlation? *Cancer*. 2000;89(7):1482–1489.
7. Nataraj V, Kandasamy D, Bakhshi S. Imatinib-induced avascular necrosis of femur in childhood chronic myeloid Leukemia. *Pediatr Hematol Oncol*. 2014;31:268–270.
8. Yassin M, Moustafa AH, Nashwan AJ, et al. Dasatinib induced avascular necrosis of femoral head in adult Patient with Chronic Myeloid leukemia. Clinical Medicine Insights. *Blood Disorders*. 2015;8:19–23.
9. Smith DW. Is avascular necrosis of the femoral head the result of inhibition of angiogenesis? *Med Hypotheses*. 1997;49(6):497–500.
10. Moon JY, Kim BS, Yun HR, et al. Rheology of leukocytes, leukocyte suspensions and blood in leukemia possible relationship to clinical manifestations, Korean. *J Intern Med*. 2005;20(3):255–259.