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Review

Avascular necrosis in patients with chronic myeloid leukemia: A systematic review

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Abstract. *Objective:* Avascular necrosis (AVN)has been encountered in hematological malignancies; nonetheless, AVN is extremely uncommon in patients with chronic myeloid leukemia (CML). This review aims to describe the pathophysiology, clinical characteristics, and outcomes of AVN in CML. To our knowledge, this is the first systematic review of this topic. *Methods:* We searched PubMed and Google Scholar for the case reports and series of patients with CML who developed AVN from inception to July 2021. *Results:* We found 21 cases of AVN in CML patients,17 cases with avascular necrosis of the femoral head (AVNFH), and four cases with osteonecrosis of the jaw (ONJ). The median age was 39 years with an almost equal distribution between males and females (ratio of 1:1). AVN related to CML management has been linked to tyrosine kinase inhibitors (TKIs) and standard interferon-alpha (IFN-α) therapies. Only six (out of 17) patients who developed AVN of the femoral head eventually required a hip replacement, and one (out of 17) developed a recurrent episode of AVNFH. All the reported cases of CML with osteonecrosis of the jaw were associated with TKIs therapy. *Conclusion:* Clinician should consider AVN in any CML patient complaining of either hip or jaw pain. IFN-α and TKI therapies can predispose to AVN in CML patients. Further studies are required for a better understanding of this condition in CML. (www.actabiomedica.it)

Key words: Chronic myeloid leukemia, avascular necrosis, jaw osteonecrosis, interferon alpha, tyrosine kinase inhibitor.

Introduction

Avascular necrosis (AVN), also named osteonecrosis, aseptic necrosis, and ischemic necrosis of the bone is defined as the death of bone and marrow cells due to the interruption of its blood supply (1). Annually, around 20,000 people require hospital admission for treatment of hip AVN. The head of femur is the most commonly affected area; yet, other sites also can be affected, including the humeral head, knee, jaw, and small bones of the hand and foot (2). AVN is classified into atraumatic and traumatic AVN. Atraumatic AVN is more common, and it has been associated with many conditions, particularly glucocorticoids therapy and alcoholism. Other conditions, like cigarette smoking, systemic lupus erythematosus (SLE), sickle cell disease (SCD), pregnancy, decompression disease, radiation therapy, metabolic bone disorders, and vasculitis syndromes have also been linked to AVN. However, the strength of a causal relationship between those conditions and AVN differs significantly, and in some of them, the causality is based only on few case reports (3). Osteonecrosis of the jaw (ONJ) has been reported increasingly in the literature, and it is mainly attributed to bisphosphonate therapy. Other medications, such as monoclonal antibodies and tyrosine kinase inhibitors(TKI), can also be associated with ONJ (4). Localized pain is the main presenting symptom of AVN, with a minority of patients being asymptomatic in the initial stage (2). Magnetic resonance imaging

(MRI) remains the gold standard modality for diagnosing AVN, with the sensitivity reaching 100% (5). Based on both clinical and radiological features, many staging classifications have been produced to determine the extent of the disease and guide the management of AVN cases (Tables 1 and 2).

Chronic myeloid leukemia (CML), also known as chronic myelogenous leukemia, is a Philadelphia positive myeloproliferative neoplasm (MPN) characterized by the unregulated production and proliferation of myeloid cells in the bone marrow. It is characterized by a specific chromosomal defect, t (9;22) (q34; q11) or Philadelphia chromosome. CML has three phases: chronic, accelerated, and blastic (6,7). Few cases of AVN in CML patients have been reported in the literature since its inception. The exact incidence of AVN in CML is still unknown as the number of cases is limited, and lack of prospective studies assessing this condition. AVN has been described as a presenting manifestation in few CML patients, whereas, in other cases, it has been linked to CML treatment, including interferon-alpha (IFN-α) therapy and tyrosine kinase inhibitors (TKI) (8). Given the high morbidity associated with AVN, we extensively reviewed the literature to shed light on the available data focusing on the pathogenesis, clinical characteristics, and outcomes of AVN in patients with CML. To the best of our knowledge, this is the first systematic review that includes all the reported cases of AVN in CML patients.

Methods

Study design and literature search

We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1). We searched the medical literature through PubMed and Google Scholar for all the relevant articles to our review using the following terms either alone and/or in combination: "AVN ", "avascular necrosis", "osteonecrosis", "aseptic necrosis", "atraumatic necrosis", "avascular necrosis of femoral head", "AVNFH", "osteonecrosis of the jaw", "ONJ", "chronic myeloid leukemia", "chronic myelocytic leukemia", "chronic myelogenous leukemia", and "CML".

Eligibility criteria

Search-related English publications of case reports and series that describe AVN in CML patients from inception till July 2021 were included in this systematic review. Articles in the grey literature and non-English language publications were excluded.

Table 1. Revised Association Research Circulation Osseous (ARCO) Staging System for AVNFH (9).

Stage	Clinical description
I	X-ray is normal Either magnetic resonance (MRI) or bone scan is positive
II	X-ray shows subtle signs of osteosclerosis, focal osteoporosis, or cystic change in the femoral head No evidence of subchondral fracture, fracture in the necrotic portion, or flattening of the femoral head
III	Fracture in the subchondral or necrotic zone as seen on x-ray or computed tomography (CT) scan IIIa (early): femoral head depression ≤ 2 mm IIIb (late): femoral head depression > 2 mm
IV	X-ray evidence of osteoarthritis with accompanying joint space narrowing, acetabular changes, and/or joint destruction

Table 2. International Task Force on Osteonecrosis of the Jaw staging system (10).

Stage	Clinical description
I	Asymptomatic Exposed bone on mandible or maxilla No evidence of significant adjacent or regional soft tissue inflammation or secondary infection
II	Painful Exposed bone on mandible or maxilla Adjacent or regional soft tissue inflammation or secondary infection
III	Painful Exposed bone on mandible or maxilla Adjacent or regional soft tissue inflammation or secondary infection Extraoral fistula or oral antral fistula or radiographic evidence of osteolysis extending to the inferior border of the mandible or the floor of the maxillary sinus

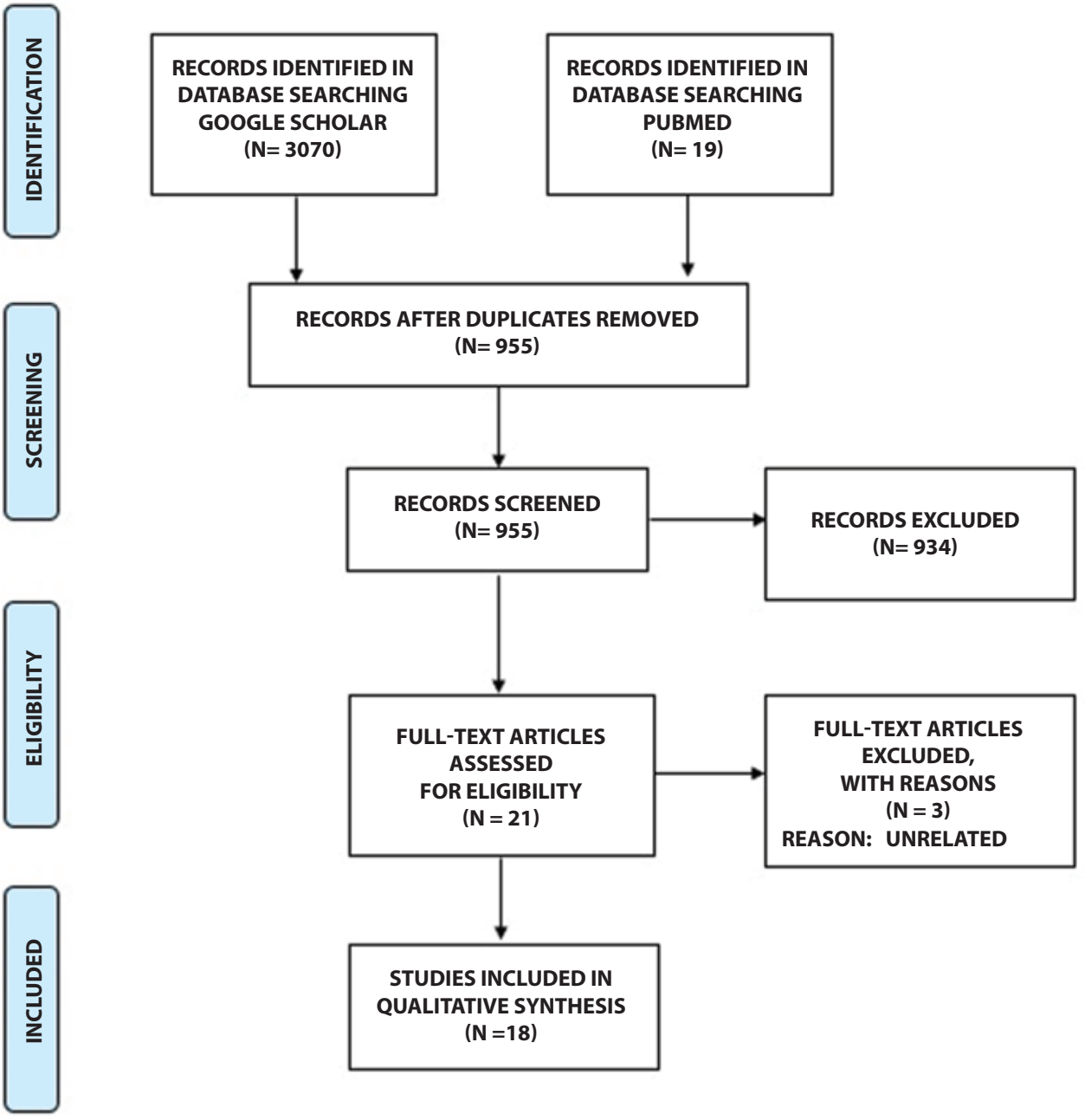

Figure 1. The PRISMA flow diagram of the study selection process.

Screening records

Results of the literature search were screened for eligibility by readings the titles and abstracts of the retrieved records. Then, we screened the full text of the eligible articles. Two authors analyzed and reviewed all screened articles individually (AFA and HNA).

Data extraction

We extracted the following data from each case:

1. The patient characteristics including age, sex, ethnicity, and duration of CML.
2. Hematological parameters on presentation with CML.

3. Site of AVN and radiological stage (if applicable).
4. Management and outcomes of AVN.

All the obtained data from these articles are summarized in Tables 3-6.

Results

To the best of our knowledge, we found 21 cases of AVN in patients with CML (17 CML patients developed AVNFH, and four patients developed ONJ). They were reported in 18 published articles between

Table 3. Avascular necrosis of the femoral head (AVNFH) as a presenting manifestation of CML.

Patient number	Author and Ref.	Year	Age (years)	Gender and Ethnicity	Site of femoral head	Blood count	Stage of AVNFH	Intervention/outcome
1	Gipson et al. (15)	1984	17	M Caucasian	Rt	WBC 116 x 10^9/L Plt 319 x 10^9/L	N/A	Total hip replacement was performed after 9 months
2	Salimi et al.(16)	1988	9	F White	Lt	WBC 359 x 10^9/L Plt 809 x 10^9/L	N/A	Improved symptomatically after chemotherapy
3	Hanif et al. (17)	1993	8	M N/A	Lt	WBC 92 x 10^9/L Plt 1,800 x 10^9/L	N/A	Was asymptomatic 18 months after diagnosis
4	Leone et al. (18)	1996	17	M N/A	Rt	WBC 167 x 10^9/L Plt 895 x 10^9/L	N/A	The patient was put on HU, his leg was immobilized in a splint, and he was forbidden to put weight on it. At 6 weeks, he had regained full use of his hip. In month 3, a combined INF-α and cytosine arabinoside treatment was begun. One month later, AVNFH recurred. Total hip replacement was performed after total of 12 months
5	Gupta et al. (19)	2003	15	F N/A	Rt	WBC 290 x 10^9/L Plt 250 x 10^9/L	N/A	Improved symptomatically after chemotherapy
6	Kraemer et al.(20)	2003	24	F N/A	BL	WBC 310 x 10^9/L Plt 828 x 10^9/L	N/A	A borehole in each femoral head was drilled to improve the proliferation of small blood vessels. The patient was partially mobilized after six weeks
7	Moon et al.(11)	2005	21	M N/A	BL	WBC 96 x 10^9/L Plt 684 x 10^9/L	N/A	Bipolar hemiarthroplasty of the right hip joint was performed

Patient number	Author and Ref.	Year	Age (years)	Gender and Ethnicity	Site of femoral head	Blood count	Stage of AVNFH	Intervention/outcome
8	Joseph et al.(21)	2006	15	F N/A	Rt	WBC 450 x 10^9/L Plt 240 x 10^9/L	N/A	Gait and walk improved remarkably within two weeks of commencing cytoreductive therapy. However, the remaining disability was observed
9	Hughes et al.(22)	2007	11	M N/A	Rt	WBC 170 x 10^9/L Plt 569 x 10^9/L	N/A	N/A
10	Kumar et al.(23)	2013	12	F N/A	Rt	WBC 393 x 10^9/L Plt 316 x 10^9/L	N/A	The pain gradually improved over the next three months. However, limping gait was persisting at 22 months of follow-up.

Legend= AVNFH: avascular necrosis of the femoral head; CML: chronic myeloid leukemia; F: female; INF: Interferon; Lt: left; M: male; N/A: not available; Plt: platelets; Rt: right; WBC: white blood cells.

1984 and June 2021(11-28). We did not find any report describing AVN in CML in other sites apart from the femoral head and jaw. There was an almost equal distribution between male and female patients with approximately a 1:1 ratio and a median age of 39 years (ranging from 7 to 71 years). Most cases did not mention the ethnicity of the patients.

A total of ten patients had AVNFH as the initial presentation of CML (Table 3). Hip pain was the most common presenting symptom among these patients, and two of them (patients 6 and 7) had bilateral AVNFH detected by MRI. The outcomes among these patients were variable. Almost all of them achieved a significant symptomatic improvement after starting CML treatment, with some of them showing complete resolution of pain. However, persistent gait problems were reported in three cases (patients 6, 8, and 10), three patients eventually required hip replacement surgeries (patients 1, 4, and 7), and only one patient developed a recurrent AVNFH after starting chemotherapy (Interferon-alpha and cytosine arabinoside) for CML (patient 4).

A total of five patients developed AVNFH possibly associated with IFN therapy (Table 4). Kozuch et al. (12) have reported three cases of patients who developed AVNFH after receiving IFN-α. Hanif et al. (17) reported a case of IFN associated AVN during the accelerated phase of CML who died due to CMV infection after bone marrow transplantation. Also, Leone et al. described a patient who had AVNFH as a presenting manifestation of CML and had regained full use of his hip six weeks after starting treatment. Interestingly, he developed another AVNFH a month later after starting IFN and ended up with a total hip replacement. Of note, all cases associated with IFN therapy were also using hydroxyurea.

Among patients who received TKIs for CML, we found only three cases of patients who developed AVNFH associated with different TKIs (Table 5), and all developed AVNFH on the left side. Notably, blood counts were within the normal range at the time of diagnosis with AVNFH. Patient 1 developed AVNFH after receiving Imatinib for eight years. Patient 2 was started initially on Imatinib due to failure of first-line therapy then shifted to Dasatinib. AVNFH, which ended by total hip replacement, occurred in this patient despite that complete hematological response (CHR), complete cytogenetic response (CCyR), and major molecular response (MMR) were achieved. Patient 3 was also treated with Imatinib after diagnosing with CML during the chronic phase. Because of Imatinib resistance that was confirmed by mutational analysis, he was switched to Nilotinib. Nine months after Nilotinib therapy, he presented with left hip pain, and MRI confirmed AVNFH.

Table 4. Avascular necrosis of the femoral head (AVNFH) in chronic myeloid leukemia (CML) patients treated with IFN-α.

Pts.	Author Ref. and year	Age (yrs) and gender	Site	Interval from CML to AVNFH	Blood count	Interferon type and dose	Duration	Other Rx	Intervention/outcome
1	Kozuch et al.(12) 2000	22 M	BL	18 months	WBC 2.5-3.5 x 10^9/L Plt 140x10^9/L	Non-Pegylated 5 MU/day	15 months	HU, steroids x 1 week, anagrelide	After 6 months, the patient underwent right hip replacement then left hip replacement. Pegylated INF-α was initiated 5 months after bilateral. hip replacement
2	Kozuch et al. (12) 2000	45 M	BL	54 months	WBC 15 x 10^9/L Plt 120-210 x 10^9/L	N/A Varied from 10 MU – 5 MU/day	54 months	HU, busulfan and cytarabine	Pain improved significantly 10 days after stopping INF. The patient remained asymptomatic at 9 months of follow-up
3	Kozuch et al. (12) 2000	46 F	BL	6 months	WBC 8.4-18 x 10^9/L Plt 160-220 x 10^9/L	Non-Pegylated 10 MU/day	3 months	HU, cytarabine, ATRA	Hip pain improved significantly after 2 months
4	Hanif et al. (17) 1993	7 F	Rt	4 years	WBC 49 x 10^9/L Plt 1,200 x 10^9/L	N/A N/A	N/A	HU	While she was receiving INF-α as maintenance therapy, her disease entered an accelerated phase, and she reported pain in her right hip. She died of CMV pneumonia after BMT
5	Leone et al. (18) 1996	17 M	Rt	Presenting symptom and after 4 months	WBC 167 x 10^9/L Plt 895 x 10^9/L After 4 months: N/A	N/A N/A	One month	HU, cytosine arabinoside	The patient was put on HU, and his leg was immobilized in a splint. At 6 weeks, he had regained full use of his hip. In month 3, a combined INF-α and cytosine arabinoside treatment was begun. 1 month later, AVNFH recurred. Total hip replacement was performed after total 12 months

Legend=ATRA: all-trans retinoic acid; AVNFH: avascular necrosis of the femoral head; BMT: bone marrow transplant; BL: bilateral; CML: chronic myeloid leukemia; CMV: cytomegalovirus; F: female; HU: hydroxyurea; INF: Interferon; Lt: left; M: male; MU: million units; Plt: platelets; Rt: right; Rx: treatment; WBC: white blood cells. Note: ethnicity and stage of AVNFH in these patients were not available.

Table 5. Avascular necrosis of the femoral head (AVNFH) in chronic myeloid leukemia (CML) patients treated with TKI

Pts.	AuthorRef. and year	Age (yrs) and Gender	Site	Int. (§)	Blood count	Stage of AVNFH	TKI dose	Duration	Other Rx	Intervention/ outcome
1	Natarj et al. (24) 2014	12M (*)	Lt	8 yrs	WBC 5.6 x 10^9/L Plt N/A	III	Imatinib 400 mg/day; escalated to 600mg/day	8 years	None	N/A
2	Yassin et al. (14) 2015	34F (**)	Lt	3 yrs	WBC 6x10^9/L Plt 235x109/L	III-IV	Dasatinib 100 mg/day	18 months	Imatinib	Treated initially with Imatinib 400mg/day. She developed AVNFH 18 months after Dasatinib. Underwent successful total hip replacement
3	Thekkudan et al. (25) 2017	47M (*)	Lt	7 yrs	WBC 5x10^9/L Plt 335x109/L	N/A	Nilotinib	9 months	Imatinib	Treated initially with Imatinib 400 mg/day, escalated to 600 mg/day. He developed AVNFH 9 months after Nilotinib. Planned for total hip replacement

*Legend = Int (§): Interval from CML to AVNFH; AVNFH: avascular necrosis of the femoral head; CML: chronic myeloid leukemia; F: female; Lt: left; M: male; Ethnicity: * N/A: not available, ** African; Plt: platelets; Rx: treatment; TKI: tyrosine kinase inhibitor; WBC: white blood cells*

Table 6. Osteonecrosis of the jaw (ONJ) in chronic myeloid leukemia (CML) patients.

Pts	Author Ref. and year	Age (yrs) and Gender	Site	Int. (§)	Blood count/ Stage of ONJ	TKI dose	Duration	Other Rx	Intervention/ outcome
1	Nicolatou-Galitis et al.(26) 2013	71 F (*)	Lt	2 years	N/A II	Imatinib 400 mg/day, then 300 mg/day	2 years	4 years before diagnosis of CML, she received rituximab,and cyclophosphamide, vincristine, prednisone for NHL as well as alendronate and one injection of zoledronate for osteoporosis	Healed after multiple courses of antibiotics
2	Won et al.(27) 2018	66 F (*)	Rt	N/A	N/A II	Dasatinib 50 mg/day, decreased to 20 mg/day	2 years	Nilotinib, imatinib, bosutinib, ponatinib	Numerous TKI therapies were not tolerated because of adverse effects. Improved after 23 months of antibiotics
3	Okubo-Sato et al.(13) 2021	52 F (**)	Rt	10 years	N/A II	Imatinib 400 mg/day	10 years	None	Sequestrectomy and removal of the mandibular tori was performed. No recurrence at 2 years follow-up
4	Myoken et al.(28) 2021	65 M (*)	Rt	3 years	N/A II	Bosutinib 500 mg/day	2 years	Imatinib	Extensive necrotomy was done, and complete resolution was obtained at 12 months postoperatively

*Legend= (§) Interval from CML to ONJ; CML: chronic myeloid leukemia; F: female; Lt: left; M: male; N/A: not available; NHL: non-Hodgkin lymphoma; ONJ: osteonecrosis of the jaw; Rt: right; Rx: treatment; TKI: tyrosine kinase inhibitor: Ethnicity: * N/A: not available, ** Japanese.*

ONJ was reported in four cases between 2018 and 2021(Table 6). Three of them were female with ages above 50 years. All four patients developed stage II ONJ, and the right mandible was more commonly involved than the left mandible. These patients received different TKIs regimens for CML: two patients developed ONJ after Imatinib therapy (patients 1 and 3), one patient after Dasatinib therapy (patient 2), and one patient after Bosutinib therapy (patient 4). One patient had a recurrence of ONJ a year after healing (patient 1), and two patients required surgical intervention (patients 3 and 4).

Discussion

This study comprises an updated comprehensive review on the pathogenesis, demographics, and clinical manifestations of AVN in CML patients. The exact mechanism by which AVN occurs is still not well recognized. AVNFH is believed to result from multifactorial effects, including genetic predisposition, vascular supply damage due to local factors, mechanical stresses, increase in intraosseous pressure, and the impact of various metabolic diseases. It has been shown that the interruption of blood supply to the bone marrow of the femoral head can lead to the death of osteocytes and mesenchymal cells (stem cells that form bone and cartilage), resulting in the resorption of healthy bone tissue and the formation of new but fragile osseous tissue (called trabecular thinning) and occasionally collapse of the femoral head (2). Likewise, the pathophysiology of AVN in CML is also unclear. It has been proposed that leukostasis and thrombocytosis that usually accompanied CML are the main predisposing factors for AVN. Leukemic cells and platelet aggregations in the microvascular circulation can lead to the microthrombi formation and subsequent interruption of blood supply to the areas with poor collateral circulation, particularly femoral heads (11).

It was suggested that there is a constant turnover of the vascular supplies of the femoral head due to the daily stress of weight-bearing. One effect of IFN-α therapy is inhibition of angiogenesis in the body, including the bone. Accordingly, in the presence of an angiogenesis inhibitor, neovascularization might not balance vascular turnover, leading to bone ischemia and the subsequent AVN of the bone. Of note, AVN associated with IFN-α therapy has been reported solely in CML patients (but not with other conditions), which indicates the disease itself plays the primary role in the development of AVN, and IFN-α therapy has an additive or synergetic effect (12).

Recently, AVN has been described in the era of tyrosine kinase inhibitors (TKIs) use in patients with CML. Imatinib, like IFN-α, inhibits angiogenesis, mainly through inhibition of Platelet-derived growth factor receptor (PDGFR) and c-Kit, which reduces expression of vascular endothelial growth factor (VEGF). In addition, Imatinib has a direct negative effect on the bone remodeling process. AVN has also been reported with other TKIs, and the mechanism is most likely similar to Imatinib. Hence, TKI therapy, especially Imatinib, should be considered a potential predisposing factor for AVN in CML patients (13).

Our review found that AVN in CML patients exclusively affects the femoral head and jaw (Figure 2). Also, there was an almost equal distribution between males and females with a 1:1 ratio. The most common presenting symptom was unilateral hip pain, even in the cases found to have bilateral AVN on MRI. The patients who initially presented with AVNFH (10 cases) were children and young adults, and no one exceeded 24 years old. Interestingly, CML is uncommon in children and young adults.

In most cases, the stage of AVNFH was not mentioned clearly, and only radiological descriptions were provided. WBC counts were strikingly elevated in patients who initially presented with AVNFH (above 10,0000 in most cases), whereas platelet counts were variable (Table 1) that might support that leukostasis, rather than thrombocytosis, has a significant role in the pathogenesis of AVN. As evidenced by our data, there was no reported case of AVN with Pegylated IFN-α use, which might indicate that pegylated Interferon is safer than standard Interferon, especially in patients who are at higher risk for AVN. We noted that all patients who developed AVNFH with Interferon were also received hydroxyurea, pointing to a possible synergetic effect of hydroxyurea in the development of AVN in such patients.

Concerning the three cases that developed AVNFH after TKI therapy, we noted that all of them

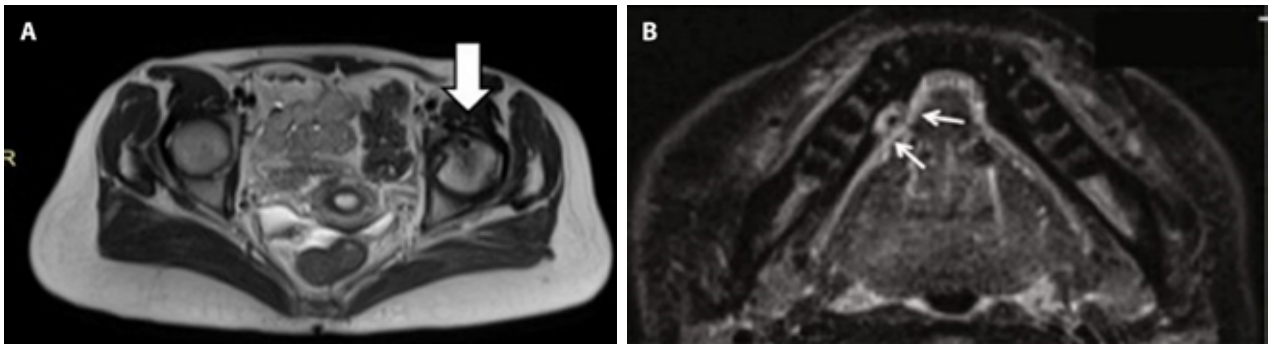

Figure. 2 MRI Images of the hips and jaw. (A) Axial view of the T2WI sequence showing multiple subarticular areas of abnormal signal intensity within the head left femur consistent with avascular necrosis (AVN) (14). (B) Axial view of T1WI sequence showing abnormal intramedullary signal intensity on the lingual side of the right lower premolar consistent with osteonecrosis of the jaw (ONJ) (13). (Both figures were reproduced from Open Access articles that are distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided that the original work is properly cited).

were in complete hematological response (CHR), which could exclude the effect of leukocytosis or thrombocytosis in the pathogenesis. Regarding OJN in CML, the period from starting TKI therapy till manifesting OJN exceeded two years duration. We are not sure why all this time is needed till the development of OJN, and further prospective study can further explain the reason. Based on our review, seven (out of 17) of patients with AVNFH eventually required surgical intervention (six patients required hip replacement). Regarding the risk of recurrence, the follow-up period in some was not mentioned, yet only one patient had a recurrence of AVNFH that occurred at the same site (Table 1, Patient 4). Given insufficient data, we could not conclude whether AVN has an adverse prognostic effect on CML clinical course. Nevertheless, we can conclude that the clinical outcomes and prognosis of AVN in patients with CML were not worse than AVN associated with other conditions. The main limitation of our review article is that those patients' data were obtained from case reports and series, so the long-term outcomes for those patients could not be appropriately assessed. Also, the number of included cases is limited (only 21 cases). Lastly, there are a lot of missing data in those case reports, including but not limited to ethnicity, staging, other risk factors for AVN, and lack of prolonged follow-up, which significantly restricted our review.

Our group is studying the unmet clinical needs in CML like cost effective analysis for second generations TKIs when used as upfront (29), the association of Tuberclosis with CML(30), the reactivation of Hepatitis B with CML(31),Ophthalmic manifestations as initial presentation in patients with CML(32), Effects of intermittent fasting on CML(33), Autoimmune hemolytic anemia and its association with different therapies in CML(34), Priapism (35)and male fertility (36), obesity (37)and obesity related surgeries in patients with CML(38) as well as the effects of environmental factors in patients with MPNs (39).

Conclusion

AVN in CML is a rare condition that carries a high morbidity rate and long-term sequela. It should be highly considered in the patient with CML who presents with either hip or jaw pain. AVN exclusively occurred in the femoral head and jaw in CML patients. Early detection and proper management of AVNFH in CML patients are essential to prevent longstanding disability. Based on our review, we can conclude that the prognosis of AVN in CML is relatively comparable to AVN related to other conditions. However, further prospective study with larger sample size is needed to clarify the different aspects of AVN in CML patients.

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