Abstract

Anemia due to iron deficiency is commonly associated with rickets, but rarely myelofibrosis was seen in infants with rickets in the hypocalcaemic phase. The aim of this review is to elucidate the mechanism of development of myelofibrosis in rickets. We reviewed the literature in PubMed with keywords myelofibrosis, hypocalcaemia and anemia. The cases diagnosed as myelofibrosis in infants with evidence of rickets were studied. Hypocalcaemia as it occurred in all the cases reported, it suggests that an association exists between myelofibrosis and hypocalcaemia possibly as a consequence of a disturbed vitamin D metabolism. We could not find another evidence to support a direct relation between low calcium per se and myelofibrosis. Vitamin D with its multiple metabolites and whose levels in our sunny communities are getting lower and lower with more associated diseases being discovered still needs to be considered. Hyperparathyroidism is another factor to be discussed together with hypophosphatemia. Vitamin D role in mast cell proliferation has to be seriously studied and basic research is necessary. Myelofibrosis in rickets seems to be caused by hyperparathyroidism whether primary or secondary. In primary hyperparathyroidism the removal the causing adenoma was followed by complete recovery of the myelofibrosis. Myelofibrosis associated with rickets is very rare but serious and need to be looked for in places where vitamin D deficiency is common.

Introduction

Vitamin D deficiency rickets presenting with hypocalcaemia and clinical rickets is not uncommon in sunny countries as it is supposed to be [1]. Factors associated with the increased prevalence of nutritional rickets in sunny countries, included housing, environmental factors and customs associated with avoidance of sun by every member of the families, especially mothers who were found to be vitamin D deficient and their infants born with vitamin D deficiency [2-4]. Iron deficiency anemia was reported among infants with rickets by Grundulis in association with rickets among Asian immigrants in the UK [5]. We have recently reported this association of vitamin D deficiency rickets with iron deficiency anemia in an all year sunny country, Saudi Arabia. It was found that out of 97 infants with rickets 45 (46.4%) were having a hemoglobin less than 11 grams [6], which is considered anemic according to WHO [7]. On reviewing the reported cases of myelofibrosis, with rickets are even very rare. No case was reported in this region since the first one in 1994 [8], although rickets and associated iron deficiency anemia are very common. On reviewing myelofibrosis associated with rickets in a trial to pick which of the biochemical abnormalities associated with rickets were the triggering agent for myelofibrosis, namely hypovitaminosis D, hypocalcaemia, hypophosphatemia or hyperparathyroidism or a combination of any. Another objective of this review is to stress on the seriousness of rachitic myelofibrosis as a life threatening condition among the highest incidence of iron deficiency anemia causes associated with rickets. Not, to miss this serious anemia and be able to diagnose it in communities with high prevalence of rickets and anemia.

The myeloproliferative disorders

Comprise several clonal hematologic diseases that are thought to arise from a transformation in a hematopoietic stem cell. The main clinical features of these diseases are the overproduction of mature, functional blood cells with a longer clinical course. The main Philadelphia chromosome negative myeloproliferative disorders are polycythemia Vera, essential thrombocythemia, and idiopathic myelofibrosis [9]. Myelofibrosis is the descriptive term referring to the excessive reticulin deposition in the bone marrow. Myelofibrosis is characterized by bone marrow fibrosis and is very rare in children. This fibrosis of the bone marrow means the marrow is not able to make enough normal blood cells, leading to anemia, bleeding problems, and a higher risk of infections.

Classification of myelofibrosis

Myelofibrosis in children could be classified into a primary where there is no associated disease or predisposing factor. Another group is secondary myelofibrosis in which a disease or a precipitating factor is preceding or associated with it [10]. In the secondary myelofibrosis reported in children and not related to malignancy there is a group related to vitamin D and related hormones; these are: vitamin D deficiency [11], renal osteodystrophy [12], and chronic renal failure.

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and hyperparathyroidism and osteoporosis [13], and Vitamin D dependent type 11 [14].

Another group of secondary myelofibrosis of children not by malignant group and not related directly to vitamin D includes: tuberculosis [15], visceral lishmaniasis [16], systemic lupus erythromatous [17], sickle cell anemia (a single case report) [18], Juvenile rheumatoid arthritis [19], Langerhans cell histiocytosis [20], hemophagocytic lymphohistiocytosis [21], Fanconi anemia [22], and Gray platelet syndrome [23]. Idiopathic myelofibrosis was reported by Say and Berkel in 1964 [24].

Juvenile idiopathic myelofibrosis has a variable outcome, some with spontaneous remission [25-27].

The Association between Myelofibrosis and vitamin D deficiency

A PubMed search with key words myelofibrosis and vitamin D deficiency revealed 33 publications, only 13 of them were having myelofibrosis and vitamin D deficiency rickets together. In this communication, I am reviewing vitamin D deficiency associated myelofibrosis in a trial to discover precipitating factors with the objective of preventing this serious although rare complication of rickets. Also trying to find which of the biochemical abnormalities are or is the triggering agent for the myelofibrosis. The association between myelofibrosis and vitamin D deficiency was first reported by Coopsenburg in a child with features of rickets in 1966 [28], although similar features of anemia known as Von Jacks anemia was known since 1935, but its relation to rickets was denied [29].

Rachitic Myelofibrosis: Clinical and biochemical findings

The cases with myelofibrosis and vitamin D deficiency rickets are summarized in the Table 1 in a chronological order [28-40]. Details of clinical and biochemical findings are shown in the Table 1.Everybody was male except the identical twins who were females and both were having myelofibrosis and rickets and responded to treatment with vitamin D and calcium [33]. The age at presentation varied from 5 to 10 months with a mean age of 6.5 months. Everybody presented with pallor and found to have hepatosplenomegaly at presentation and everyone had different degrees of clinical evidence of rickets. Everyone had a low hemoglobin ranging from 3 to 9.7 mg% with a mean level of 6.7mg%. Platelets and white blood cell levels were also low. Dry bone marrow aspiration was suggestive of myelofibrosis, which was confirmed in all with bone marrow biopsy. Everyone responded to vitamin D and calcium therapy with evidence of healing of the rickets, but the blood parameters specially leucopenia persisted in some that few of them succumbed to infection at a later age due to the persistence of leucopenia.

Hematological findings in myelofibrosis

Review of the peripheral blood smear is a key point and likely reveals several abnormalities. Dacrocytes (teardrop-shaped red blood cells) are common in myelofibrosis. Nucleated red blood cells and aniso-poikilocytosis are also frequently seen. Myelocytes and promyelocytes are present in a small proportion in most patients; blast cells may also be seen. Platelets may be large or having an unusual shape. In rare cases, the platelet count may be elevated (thrombocytosis). All the reported cases were confirmed as myelofibrosis by the characteristic blood picture and confirmed by bone marrow biopsy. The presence of myelofibrosis together with clinical and biochemical features of rickets in all these infants cannot be by chance, warranting the need for reviewing the relation of myelofibrosis and each of the biochemical abnormalities, in a trial to pinpoint which of the rachitic biochemical abnormality is the triggering agent of the myelofibrosis.

The role of, hypocalcemia, hyperparathyroidism and hypovitaminosis D hypophosphatemia in the development of myelofibrosis:

Hypocalcemia: Hypocalcemia is a constant feature in all cases of myelofibrosis shown in the Table 1, with a mean level of 5.6 mg% (ranging from 4 to 10 mg%). Although hypocalcaemic convulsions are a common presenting feature of rickets in the first year of life, only very few develop myelofibrosis. Naggar et al. [38], reported that on observation of a case of myelofibrosis with myeloid metaplasia of the liver and spleen associated with hypocalcemia led them to investigate whether this association was fortuitous. They retrospectively analyzed the data of 30 patients with myelofibrosis and identified nine patients with hypocalcemia out of 22 in whom the plasma calcium level corrected for serum protein could be obtained, i.e. a prevalence of hypocalcemia at 41%. The spleen was significantly larger in the patients with hypocalcemia than in those with normal plasma calcium level. They suggested that the hypocalcemia was related to the duration of the disease. In five patients with hypocalcemia, biological and/or morphological evidence of osteomalacia was found. They concluded that an association exists between myelofibrosis and hypocalcemia, possibly as a consequence of a disturbed vitamin D metabolism. We could not find another evidence in the literature to support a direct relation between low calcium per se and myelofibrosis.

Hyperparathyroidism: All cases of myelofibrosis, were having hyperparathyroidism, as part of biochemical changes in rickets, this might suggest a specific role for PTH in the development of myelofibrosis. To discuss this hypothesis, we reviewed the literature starting with this case report [39]. A female presented with fatigue, and bilateral knee pain and gait disturbance. Primary hyperparathyroidism was diagnosed together with splenomegaly hypovitaminosis D and anemia. Bone marrow biopsy revealed myelofibrosis. A parathyroid adenoma was diagnosed and surgically excised. As early as three months after the operation, hematologic parameters improved along with bone markers without any other intervention. The control bone marrow biopsy demonstrated well marked regression in marrow fibrosis. Her spleen also decreased in size. This complete recovery indicates that her myelofibrosis was the result of primary hyperparathyroidism due to the adenoma. Akaya et al. [40], reported primary hyperparathyroidism (PHP) and myelofibrosis in a 15-year-old boy who presented with generalized weakness, vomiting, and pallor. A parathyroid adenoma was detected on the left distal parathyroid gland. PHP was diagnosed together with hepatosplenomegaly and pancytopenia. Bone marrow biopsy revealed grade 3-4 reticulin fibrosis. As early as 2 months after the left distal parathyroidectomy, hematologic parameters improved without

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any other intervention. His liver and spleen also gradually decreased in size. They concluded that the pancytopenia was because of bone marrow fibrosis resulting from primary hyperparathyroidism, suggesting that physicians should consider myelofibrosis secondary to primary hyperparathyroidism as a cause of pancytopenia in hypocalcemia patients, in spite of its rarity [41]. It is suggested that parathyroid hormone (PTH), when excessive, interferes with normal erythropoiesis by suppressing the erythropoietin receptors on erythroid progenitor cells in the bone marrow. Calvi [42], reported that parathyroid hormone (PTH), through activation of the PTH/PTHrP receptor (PTH1R) in osteoplastic cells, could alter the hematopoietic stem cell (HSC) niche resulting in HSC expansion in vivo and in vitro and improving dramatically the survival of mice receiving bone marrow transplants. This alteration may be the fibrosis observed in association with myelofibrosis. Recently, Brunner [43], found that primary hyperparathyroidism is associated with increased circulating bone marrow-derived progenitor cells, in addition to the (PTH) were shown to support survival of progenitor cells in bone marrow. The release of progenitor cells occurs in physiological and pathological conditions was shown to contribute to neo-vascularization in tumors and ischemic tissues. Further, Bahadada et al. [44], stated that anemia is common in patients with symptomatic PHPT, and was associated with marrow fibrosis in the majority of the patients who underwent bone biopsy. Both anemia and marrow fibrosis improved after curative parathyroidectomy, but improvement in anemia was noticeable only in those who had marrow fibrosis at presentation. Ohishi et al. [45], while studying, myelofibrosis associated with hyperparathyroidism, performed a study in mice proving that: the BM is a permissive microenvironment for the differentiation of fibrocytic cells and raised the possibility that these cells could contribute to the pathogenesis of BM fibrosis. Further Sikole [46], suggested that parathyroid hormone (PTH), when in excessive amounts, and interferes with normal erythropoiesis by down regulating the erythropoietin receptors on erythroid progenitor cells in the bone marrow. Therefore, physiologic concentrations of EPO can no longer sustain normal red cell counts, so normocytic and normochromic anemia ensues. In primary hyperparathyroidism (HPT), this effect is observed with very high concentrations of PTH. In secondary HPT during chronic renal failure, this effect is more pronounced because erythropoietin synthesis is impaired. From these data, we can say that myelofibrosis in rickets is caused by secondary hyperparathyroidism, as it was reported in primary hyperparathyroidism, especially in the cases of parathyroid adenoma showing complete recovery postoperatively. (Myelofibrosis associated with chronic renal failure is also having associated hyperparathyroidism with almost non-functioning vitamin D. In this situation, it can be stated that hypovitaminosis D and hyperparathyroidism have a synergistic role in the development of myelofibrosis, that there is a critical level of each of the metabolites that precipitates the myelofibrosis supported and explained by that only few of vitamin D deficiency cases with hyperparathyroidism will develop myelofibrosis.

Hypovitaminosis D: The relation of hypovitaminosis D with myeloproliferative diseases was studied by Pardanani et al. [47], who looked into the clinical and prognostic relevance of low plasma levels of 25-hydroxyvitaminD (25OH D) in myeloproliferative neoplasms (MPN) and Myelodysplastic syndromes (MDS). There were no significant correlations between 25 (OH)D insufficiency, or severe deficiency, and a variety of clinical or laboratory variables

### Table 1: Reported cases of Myelofibrosis with Rickets (1966-2013).

| Reference no | Yr | Count | Journal | AGM. | Ge | Fe | PR | L | S | Ca | Phi | VitD | PTH | AIK | Hb | wbc | P | hemD Outcome |
|--------------|----|-------|---------|------|----|----|----|---|---|----|-----|------|-----|-----|----|----|---|-------------|
| 1-Cooberber (28) | 1966v | Canada | Ca jp | 8 | m | bf | Pale | +5 | +7 | 10.2 | 2.7 | L | H | H | 9.7 | 77 | 45 | Leuocerythroidastic Rec 1/8m |
| 2-Rao (29) | 1983 | India | A J p hem | 9 | m | bf | Pale | + | + | L | L | L | H | H | 350 | 6 | 5.3 | 90 | Recovered |
| 3-Yetgin (30) | 1989 | Turkey | J p | m | bf | Pale | + | + | L | L | L | H | H | L | L | Rec | Recovered |
| 4-Al-Eissa (8) | 1995 | S A | Acta Haematol. | 6 | m | bf | Pale | + | + | L | L | L | H | H | L | L | Rec died | Inf |
| 5-Stephan (31) | 1999 | France | EUR J Pediat. | 5 | m | bf | Pale Inf | + | + | L | L | H | H | H | L | L | Recovered |
| 6-Atig (32) | 1999 | Pakistan | J Pak Med Ass | 5 | m | bf | + | + | L | L | L | H | H | 8 | 10 | |
| 8-Ozsoya (33) | 2003 | Turkey | EU J Ped | inf | m | bf | Pale | + | + | 7.1 | 2.3 | L | 33 | 2115 | 7.8 | 10.5 | 125 | Rec 2y |
| 9-Gruner (34) | 2003 | USA | J ped hem onc | inf | m | bf | Pale | + | + | L | L | L | H | H | L | L | |
| 10-Yetgin (35) | 2004 | Turkey | Tur Ped J | 5 | m | pale | + | + | 8 | 1.5 | L | H | 437 | 6.7 | 4.7 | 62 | recovered |
| 11-Balkan (36) | 2005 | Turkey | J Int Med Res | 6 | m | bf | Pale | + | + | 4.8 | 2.2 | 6 | 21 | 3364 | 6.5 | 11 | 100 | Recover 1y |
| 12-Balasubramanian (37) | 2007 | India | Indian Pediatr. | 6 | m | bf | Pale | + | + | 7.9 | 2.9 | L | 180 | 2697 | 3.9 | 3.7 | 65 | Rec died inf 8m |
| 13-Kamien (38) | 2007 | Aust. | J Paed Ch. Health | q | ff | Pale | + | + | 5.5 | 2.2 | 5.5 | L | 49.11 | 967 | 7.8 | L27 | L | Rec twins |
| 14-Bhakthi (39) | 2010 | India | IND J P | 10 | m | bf | Pale | + | + | 7.2 | 2 | 9 | ND | 1200 | 3 | 164 | 90 | |
| Mean | 4 turk Indian (31) | 6.5 | + | + | L | L | L | VH | H | L | L | | | | | |

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in PMF, MDS, or PV. They concluded that while hypovitaminosis D is relatively common in MPN and MDS, its clinical relevance for prognosis is limited. As I have seen many cases of vitamin D deficiency over thirty years presenting with a wide range of presentations, it is rare to see myelofibrosis in infants with rickets. This makes it unlikely that the vitamin D per se is causing myelofibrosis, it might be contributing partially, through its role in hypocalcemia leading to hyperparathyroidism. An observation by Visinjic [48], demonstrated a role of osteoblasts in hematopoiesis and provided a model to study interactions between the mesenchymal and hematopoietic compartments in the marrow. Together with the decrease in bone marrow hematopoiesis, active extra-medullary hematopoiesis was observed in the spleen and liver, as measured by an increase in peripheral HSCs and active primary in vitro hematopoiesis. After withdrawal of GCV, osteoblasts reappeared in the bone compartment together with a recovery of medullary and decrease in extra-medullary hematopoiesis. These observations directly demonstrate the role of osteoblasts in hematopoiesis and provide a model to study the interactions between the mesenchymal and hematopoietic compartments in the marrow. Also Koeffler [49], have demonstrated findings suggesting that 1,25-(OH)2D3 may play a role in hematopoiesis. Also, it was suggested by Yetgin [23] that in his case the improvement of rickets and hematological findings with treatment at the same time raises the possibility of vitamin D acting directly upon the same targets or upon different targets at the same time or the presence of interaction between two targets. They stressed again that further studies were warranted to clarify the mechanisms of development of myelofibrosis in vitamin D deficiency which is a fact shown by all these cases reported although it is rare. In a community with high prevalence of vitamin D deficiency we think this subject needs further studies.

Conclusion

Myelofibrosis associated with rickets is a rare entity that paved its way through a biochemical triad of hypocalcemia, hyperparathyroidism and hypovitaminosis D watched by hypophosphatemia. Being hard to pinpoint which of the three abnormalities is the triggering factor yet it seems it is most likely precipitated by hyperparathyroidism as it is the only abnormality that is coherent with the events reported. Also, because it occurred in hyperparathyroidism due to an adenoma and cured postoperatively. The response to vitamin D therapy is through its role in improving serum calcium absorption correcting calcium level and normalization of parathormone level seems to be what cures the myelofibrosis. Further studies are asked to pick up myelofibrosis at an early stage among the highest percentage of anemia in the population of rickets in our residential field. But what about vitamin D with its role in mast cell proliferation has to be seriously studied and basic research is necessary. Myelofibrosis in rickets is most likely caused by hyperparathyroidism whether primary or secondary, but further studies are needed. We conclude by Yetgin [23], stating that vitamin D could exert its influence not only by stem cell differentiation but also by proliferation. In any case, vitamin D inadequacy is not entirely a disease of the bones, but serious myelofibrosis can occur and might be fatal and it is most likely precipitated by the hyperparathyroidism, but in that location is another factor or factors that might play a part as well.

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