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Research paper

Associations of myeloid hematological diseases of the elderly with osteoporosis: A longitudinal analysis of routine health care data

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ABSTRACT

Background: Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML) are hematological stem cell diseases mainly of the elderly. Studies indicate a close relationship between bone metabolism and hematopoietic stem cells within the osteo-hematopoietic niche. However, it remains unclear how the disturbed interaction within the osteo-hematopoietic niche affects bone homeostasis in MDS and AML patients.

Methods: We utilized data of a large German statutory health insurance of approximately 2 million persons living in the German federal state of Saxony. Applying case definitions based on diagnosis, procedures and prescriptions we identified prevalent and incident cases with MDS, AML and osteoporosis (OSP) in persons aged ≥60 years. We applied time-to-event analyses to determine the relationship of MDS and AML with OSP with a specific focus on temporality.

Results: Among all individuals aged ≥60 years (n = 891,095), 2.62% (n = 23,326), 0.14% (n = 1219) and 0.10% (n = 893) were identified with incident OSP, MDS and AML, respectively. The risk of incident OSP was significantly increased in patients with prevalent MDS (sex and age-adjusted model: HR = 1.87, 95%CI: 1.51–2.23). Conversely, patients with prevalent OSP had an increased risk to be diagnosed with incident MDS in the adjusted model (HR = 1.42, 1.19–1.65). For AML no significant associations were observed (adjusted models: inc. OSP with pre. AML; HR = 1.06, 0.65–1.47; inc. AML with pre. OSP; HR = 0.82, 0.41–1.23).

Discussion: Our results could indicate a clinically relevant relationship between MDS and OSP in elderly patients, most likely resulting from a disturbed microenvironment within the osteo-hematopoietic niche. An alternative, non-causal explanation that MDS is caused by the medication prescribed for OSP can be partially ruled out, as the association between the two diseases remains if incident OSP cases are considered in patients with pre-existing MDS. These results need to be confirmed within other prospective studies and may allow then for comprehensive strategies for the prevention, early detection and clinical care of patients with MDS and OSP.

1. Introduction

With 27.5 million patients in Europe osteoporosis (OSP) is one of the most frequently occurring disorders in elderly people leading to an increased risk of fractures and falls due to progressive loss of bone strength [1]. 3.5 million incident fractures, possibly related to OSP, were estimated for the year 2010 [1] in Europe. Myelodysplastic syndromes (MDS) represent a group of common hematological malignancies of the elderly caused by heterogeneous clonal disorders of hematopoietic stem and progenitor cells (HSPC). MDS patients are frequently suffering from fatigue due to anemia and are at high risk for infections and bleeding [2,3]. The crude incidence of MDS in Europe ranges between 3.2 and 12.6 cases per 100,000 per year [4–6] depending on the study population. MDS incidence increase significantly

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in patients aged above 70 years, especially for men [7].

MDS patients are also at risk for progression to secondary acute myeloid leukemia (AML) [8]. With 3.4 new cases per 100,000 persons per year, AML is the most frequent type of leukemia in adults. AML comprises the lowest survival rate among all types of leukemia with a median survival time of 11–20 weeks [9].

Several preclinical studies indicate a central role of the bone and its microenvironment in regulating hematopoiesis and in particular the pathogenesis of MDS [10–13]. Bone-resorbing osteoclasts as well as lymphatic and myeloid cells are originating from the hematopoietic stem and progenitor cells located in the osteo-hematopoietic niche within the bone marrow. This bone marrow niche also contains mesenchymal stem cells (MSC) generating precursors for bone-forming osteoblasts [14] which play a central role in the regulation of osteoclasts. The mutual interactions between MSC and HSPC are essential for the differentiation of osteoblasts and the cell fate determination [15]. However, perturbations in the interaction of MSC and HSPC can disturb stem cell differentiation and disrupt tissue homeostasis resulting in malignant diseases such as MDS and AML [13].

In the process of aging, bone formation as well as hematopoiesis are affected due to alterations in the bone marrow niche leading to a reduced stability in bone and a decreased cell number in the blood [8,16]. Respective associations have been shown in observational studies focusing on bone marrow density and bone mass in association with blood cell counts, hemoglobin levels and anemia [17–20]. These studies are, however, based on potentially selective study populations and are exclusively observing cross sectional associations. So far, no longitudinal studies are available investigating associations of manifested diseases of the bone with MDS and AML. We hypothesize that OSP and MDS as well as AML are significantly positively associated with each other in patients aged 60 years or older.

2. Methods

2.1. Definition of “prevalence” and “incidence”

The (period) prevalence (frequency of disease) indicates the proportion of people in our defined population who is affected by OSP and/or MDS/AML within the time-period 2008–2014, no matter if the onset of the disease was before the observation period or within. This differs from the incidence which is the number of newly diagnosed OSP or MDS/AML cases within our defined population of elderly patients over the time-period 2009–2014 (patients with cases in 2008 were excluded).

2.2. Study design

We conducted a large population-based, prospective cohort study to systematically investigate the relationship between OSP and MDS/AML with a specific focus on the timing of manifestation of these disorders.

2.3. Study population

The analysis included patients born before 1951 restricting the study sample to patients being 60 years or older during the observation period. Patients were excluded from the analysis if they had a diagnosis of bone metastasis (ICD-10 C79.5) within one year before the diagnosis of osteoporosis. The group was excluded to ensure a valid case definition for osteoporosis, since a bone marrow puncture can also be used in the context of bone metastasis. For a valid identification of cases with OSP, MDS and AML we developed internal case validation methods, which were in accordance with the recommendations of the Working Group for the Survey and Utilization of Secondary Data representing the German standard for Good Practice in Secondary Data Analysis [21]. All case definitions were based on the respective coding systems for diagnosis (ICD-10-GM), procedures (Uniform Value Scale (EBM) and German modification of the International Classification of Procedures in Medicine (OPS)) as well as prescriptions (Anatomical Therapeutic Chemical code (ATC) and pharmaceutical registration numbers (PZN)).

Table 1
Definitionof prevalent and incident cases of Myelodysplastic Syndromes (MDS), Acute Myeloid Leukemia (AML) and Osteoporosis (OSP).

Case definitions
Myelodysplastic Syndromes MDS (prevalent)
1x inpatient diagnosis (ICD-10 D46) in 2008 or
2x outpatient diagnosis (ICD-10 D46) in 2008 from hematologist and bone marrow puncture within 3 quarters afterwards
Acute Myeloid Leukemia AML (prevalent)
analogous to MDS, but based on ICD-10 C92 diagnosis
Osteoporosis OSP (prevalent)
2x outpatient diagnosis (ICD-10 M80-82) in 2008 (different quarters)
plus one prescription of bisphosphonate (ATC M05BA) or denosumab (ATC M05BX04)
Identification of incident cases
respective cases were excluded in 2008 and
aforementioned case definitions were used for MDS, AML, or OSP respectively
within the observation period 2009–2014

To be identified with *prevalent* MDS, patients had to have at least one inpatient diagnosis of MDS (ICD-10 D46) or at least two confirmed outpatient diagnosis of MDS within two different quarters of one year at a hematologist as well as a bone marrow puncture (OPS Code 1-424 or EBM 02341) within the following three quarters after first MDS diagnosis. The case definition for AML corresponds to the definition for MDS in terms of timing, procedures and medical specialists, but is based on the respective diagnosis for AML (ICD-10 C92).

Cases with *prevalent* osteoporosis were identified using outpatient data and the ICD-10 Codes M80-M82 which had to be documented at least twice within two quarters of one year. In addition, at least one prescription of *bisphosphonate* (ATC M05BA) or *denosumab* (ATC M05BX04, trade name Prolia, Amgen, Thousand Oak, CA, USA) had to be documented.

For the identification of *incident* cases, case definitions from above hold true. In addition, a disease-free time interval of at least one year (sensitivity analysis 3 years) was a mandatory requirement (see Table 1). In order to identify incident cases, all beneficiaries had to be insured continuously during the base period.

2.4. Data

In Germany, approximately 90% of the population is covered by statutory health insurances. We used routine health care data from the AOK PLUS, a large statutory health insurance in Saxony (area ~18.000 km^2, population ~4 Mio.), which approximately covers the half of the local general population [22]. The data include information from inpatient and outpatient care with respect to diagnosis, procedures and prescriptions as well as socio-demographic information of the insured population such as age and sex. Age distribution and sex-ratio of the AOK PLUS beneficiaries in Saxony are comparable to the Germany-wide population [22]. Data were available from 01/2008 until 12/2014. The study protocol was registered in the database “Versorgungsforschung Deutschland” [23] prior to data analysis.

2.5. Ethics approval and consent to participate

The present analysis is based on secondary data from the health insurance company AOK PLUS, which were collected for the purpose of billing medical services. The data was available for us in anonymous form, so that no conclusions can be drawn about the individuals. The data are not publicly accessible. There was no influence whatsoever on the policyholders and no intervention was carried out. It is therefore a purely observational study. Informed consent and ethical approval are