Leukemia Research Reports 2 (2013) 61–63

Contents lists available at ScienceDirect

Leukemia Research Reports

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

Case report

Myeloproliferative neoplasms in five multiple sclerosis patients ☆

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ARTICLE INFO

Article history:
Received 13 May 2013
Received in revised form
24 June 2013
Accepted 25 June 2013
Available online 31 July 2013

Keywords:
Essential thrombocythemia
Polycythemia vera
Myelofibrosis
Multiple sclerosis
Interferon

ABSTRACT

The concurrence of myeloproliferative neoplasms (MPNs) and multiple sclerosis (MS) is unusual. We report five patients from a localized geographic area in Denmark with both MS and MPN; all the patients were diagnosed with MPNs in the years 2007–2012. We describe the patients' history and treatment. A potential link between MS and MPNs has not been previously recognized. This observation calls attention to potential environmental factors and/or previously unrecognized genetic factors predisposing these patients to both MS and MPNs.

1. Introduction

Myeloproliferative neoplasms (MPNs) are stem-cell-derived disorders that cause overproduction of one or more of the formed elements of the blood. MPNs include chronic myelogenous leukemia (CML) and the Philadelphia-negative MPNs: polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF) and unclassifiable MPN (MPN-U) [1]. A gain-of-function mutation in the gene for Janus kinase 2 (JAK2), the JAK2 V617F mutation, is found in the majority of patients with PV and about half of patients with ET and PMF. The etiology of MPNs is unknown, but an increased risk of MPNs has been found in patients with a family history of MPNs, prior autoimmune and/or inflammatory conditions and exposure to certain chemicals [2]. Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system of unknown etiology. MS can be divided into relapsing-remitting, primary progressive and secondary progressive MS, depending on the clinical course [3].

Here we describe four cases of MS-patients that subsequently developed MPNs and one case of a MPN-patient that developed MS. All five patients were referred to our centers, in the period of 2007–2012. Two of the patients were diagnosed with PV, the third with MPN-U, the fourth with ET and the fifth with PMF. All patients were diagnosed with MS according to the McDonald diagnostic criteria and with MPNs according to the WHO criteria [1,3].

2. Case stories

Case reports with patient characteristics are summarized in Table 1.

3. Discussion

The concurrence of MS and MPN in our series of patients is unusually high with four patients in the Roskilde MPN-population alone. The annual incidence rate of MS in Denmark is about 4.44 per 100,000 population, being 37% higher in females than males [4]. The true incidence of MPNs in Denmark is unknown but is estimated to be approximately 0.5–1.5 per 100,000 per year for ET and PV, respectively, and about 0.5 per 100,000 per year for PMF. Only one case report has previously described the concurrence of a Philadelphia-negative MPN and MS, which developed during the course of ET [5]. A potential link between MS and myeloid cancer has not been previously recognized. A population-based study from 2010 found no association between previous MS diagnosis and development of MPNs [6]. For these reasons, the concurrence of four patients with both MS and MPN in the Roskilde MPN-population, and an additional patient in another hematological

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http://dx.doi.org/10.1016/j.lrr.2013.06.004

Table 1
Patients characteristics and treatment.

Patient	Sex	Type of MPN	Age at MPN diagnosis	JAK2 V617F mutation	Blood analysis at diagnosis	Bone marrow biopsy at diagnosis	Type of MS	Age at MS diagnosis	MRI	MS treatment	MPN treatment
1	F	MPN-U	47	–	Hb 13.4 g/dl Hct 0.43 TLC 16.8×10^9/l Platelet count 546×10^9/l CRP 24 mg/l LDH 179 U/L	Moderately hyperplastic Slight increase in megakaryocytes Iron status normal RF grade 1	RR	38	Several diffuse areas of increased T2 signal in the brain and the cervical spine	Glatiramer acitate IFN-beta	IFN-alpha
2	F	PV	38	+	Hb 14.5 g/dl Hct 0.43 TLC 8.7×10^9/l Platelet count 514×109/l	Moderately hyperplastic Lively erythropoiesis Normal myelopoiesis Discrete megakaryocytosis Iron-depleted RF grade 0	RR	26	Numerous paraventricular hyperintense areas, plaques in the brain stem and in both cerebral hemispheres	IFN-beta Glatiramer acitate Mitoxantrone Natalizumab	No treatment
3	M	PV	57	+	Hb 20.8 g/dl Hct 0.60 TLC 12.0×10^9/l Platelet count 485×10^9/l	Slightly hyperplastic Slightly increased megakaryocytosis Lively erythropoiesis Iron-depleted	PP	45	Multiple hyperintense lesions in the white substance of the brain	No treatment	Hydroxy-urea
4	M	ET	46	+	Hb 14.8 g/dl HCT 0.42 TLC 13.4×10^9/l Platelet count 829×10^9/l Plasma EPO 2.8 U/L	Hypercellular Lively myelo- and erythropoiesisIncreased number of megakaryocytes Low iron status	RR	46	>25 hyperintense lesions in the white substance periventricular, in corpus callosum, left hemisphere and pons.	IFN-beta	Anagrelide
5	F	PMF	69	+	Hb 12.4 g/dl Hct 0.39 TLC 40.5×10^9/l Platelet count 992×10^9/l LDH 529 U/l Plasma EPO <0.1 U/L	Moderately hyperplastic Lively myelopoiesis Increased number of polymorphic megakaryocytes Low iron status RF grade 3	PP	55	Multiple hyperintense lesions in the brain stem, cerebellum and corpus callosum.	No treatment	Hydroxy-urea

EPO, erythropoietin; ET, essential thrombocytosis; Hb, hemoglobin; Hct, hematocrit; JAK2: Janus kinase 2; LDH, lactic acid dehydrogenase; MPN, myeloproliferative neoplasm; MPN-U, myeloproliferative neoplas. m unclassified; MS, multiple sclerosis; PMF, primary myelofibrosis; PP, primary progressive; PV, polycythemia vera; TLC, total leukocyte count; RF, Reticulin fibrosis; RR, relapsing-remitting.

department in the same geographic area, is certainly highly unexpected.

The association between chronic inflammation and subsequent cancer is well established, and chronic inflammation is thought to have a role in both the initiation and promotion of neoplasms [7]. MS is a relapsing inflammatory disease of the central nervous system that leads to damage of nerves and axons. Dysregulation of the immune system leads to activation of autoreactive lymphocytes that migrate across the blood-brain barrier and initiate the production of pro-inflammatory cytokines [8]. Chronic inflammation has been hypothesized to play a role in triggering clonal evolution in MPNs [7]. Therefore, it is intriguing to consider if chronic inflammation in our five MS patients may be involved in the development of their MPNs. In this context it is important to note that all our patients were relatively newly diagnosed – four being in the early stage (ET/PV) in the biological continuum, and one patient diagnosed with myelofibrosis. Many patients with MPNs have most likely had their cancer for several years before diagnosis, elevated leukocyte and platelet counts being considered "reactive". Accordingly, the inflammation drive – having potentially triggered the two illnesses – may have been ongoing for several years before the clinical diagnosis of MPNs and MS. Other possibilities to consider in regard to the concurrence of MPNs and MS are hematological side effects of the MS treatment, environmental or genetic factors.

Finally, it is highly interesting to note that human endogenous retroviruses have been suggested to play a role in the etiology of both MS and MPN [7,9]. Supporting this notion, both MS and MPN are treated with type 1 interferons, which have very potent antiviral and immunomodulating effects. Indeed, IFN-alpha2 is able to induce sustained complete hematological remissions with normalization of the bone marrow even after discontinuation of interferon-alpha2 for up to three years. Accordingly, endogenous human retrovirus has most recently been proposed to be involved in the pathogenesis of MPNs [7].

In conclusion, we report for the first time the unusual concurrence of MS and MPNs in five patients from a localized geographic area in Denmark. This observation calls attention to potential environmental factors and/or previously unrecognized genetic factors predisposing these patients to both MS and MPN. It also raises the possibility that MPNs might be underdiagnosed in MS patients, since especially ET and PV patients can have discrete symptoms. This might contribute to the increased risk of both venous and arterial thrombosis in MS patients [10]. In the context that IFN-alpha and -beta interfere with virus replication it is of interest to consider if chronic inflammation – possibly elicited by virus infection – may trigger and drive MS and MPNs [7]. The susceptibility to these diseases may be dependent upon the individual haplotype which may be shared by both diseases. Further studies are needed to clarify if an association between MS and MPNs indeed exists in the Danish MS/MPN population or in distinct areas and – if so – to elucidate common factors which might explain the concurrence of two rare diseases, including environmental (e.g. chronic inflammation – a role of human endogenous retrovirus?) or genetic factors (e.g. a common JAK2 haplotype) predisposing the patients to both diseases.

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