

R E V I E W

Myasthenia Gravis and Myeloproliferative Neoplasms – Mere Association or Paraneoplastic Neurologic Syndrome: A Mini-Review

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Abstract. Myasthenia Gravis (MG) is a rare neurological condition characterized by muscle weakness that worsens after use. Myeloproliferative Neoplasms (MPNs) are disorders due to stem-cell hyperplasia characterized by an increased peripheral blood cell count, overactive bone marrow, and proliferation of mature hematopoietic cells. MPNs may be Philadelphia (Ph) chromosome-positive or Negative. A systematic review of case reports was conducted by searching PubMed, Scopus, and Google scholar to identify case reports in which there is an association between MG and MPN and know whether MG can be considered a possible neurological paraneoplastic syndrome in patients with MPNs. A total of 13 cases of MPNs associated with MG were identified. The most common type of MPN associated with MG was chronic myeloid leukemia (CML) (10 out of 13 patients). In most of the patients, MG symptoms appeared after a diagnosis of MPN was made. Considering that 10 out of the 13 patients in our cohort had positive auto-antibodies though only 4 of them had thymic hyperplasia, we hypothesize that bone marrow proliferation was responsible for the production of autoantibodies in these patients. As the clonal cell population cannot be eliminated entirely in the bone marrow even after treatment with tyrosine kinase inhibitors (TKI) in Ph +ve MPNs and JAK2 inhibitors in Ph -ve MPNS, MG can occur even in patients who are treated with these agents. A high index of suspicion is needed to diagnose it early, and treatment should be initiated immediately with steroids and anticholinergic agents. (www.actabiomedica.it)

Key words: Myasthenia gravis, myeloproliferative neoplasms, paraneoplastic neurological syndrome, polycythemia vera, essential thrombocythemia.

Introduction

Myasthenia Gravis (MG) is a rare neurological condition with a prevalence of 0.2 - 0.4 per thousand (1). It is characterized by muscle weakness that worsens after use. In most patients, initial symptoms involve the extrinsic ocular muscles (EOMs). The symptoms progress to other bulbar muscles and limb muscles, resulting in generalized MG. In 10% of the patients, symptoms remain limited to the EOMs, known as ocular MG (2). Antibodies to the acetylcholine receptor (AChR) are found in 85% of

patients with generalized MG and 50% of those with ocular MG (3). The antigenic target defines the subtypes of autoimmune MG. The most common target of autoantibodies in MG is the nicotinic acetylcholine receptor (AChR) in approximately 85% of the patients, followed by muscle-specific kinase (MuSK) and lipoprotein receptor-related protein 4 (LRP4) in about 15% (4).

Myeloproliferative Neoplasms (MPNs) are disorders due to stem-cell hyperplasia characterized by an increased peripheral blood cell count, overactive bone marrow, and proliferation of mature hematopoietic

cells (5). 2016 WHO category of MPNs includes the three major subcategories of Janus kinase 2 (JAK2)/calreticulin (CALR)/myeloproliferative leukemia virus oncogene (MPL) mutation-related MPNs: Polycythemia Vera (PV), Essential Thrombocythemia (ET), and Primary Myelofibrosis (PMF), as well as four other clinic-pathologic entities: chronic myeloid leukemia (CML), chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia, not otherwise specified (CEL-NOS) and MPN, unclassifiable

(MPN-U) [6]. PMF includes pre-fibrotic/early PMF (pre-PMF) as well (7). The diagnostic hallmark of CML is the invariable presence of the BCR-ABL1 mutation (6, 8, 9). Characteristic bone marrow morphology is required for WHO compliant diagnosis, especially in distinguishing ET from pre-fibrotic PMF and masked PV (10).

Paraneoplastic neurological syndromes (PNS) are disorders associated with cancer, not caused by direct invasion, metastasis, or treatment consequences. They are autoimmune, rare, but potentially treatable [10] and can occur before or after primary cancer diagnosis (11). The prevalence of these disorders varies with the type of cancer. PNS occurs in 2–3% of the patients with neuroblastoma or small cell lung carcinoma (SCLC) and 30–50% of the patients with thymoma. Overall, 0.5–1% of all patients with cancer have clinically disabling PNS (10). PNS are more commonly associated with solid organ malignancies and very rarely with hematological malignancies. Hematological malignancies, including myeloproliferative disorders, are more commonly associated with dermatological paraneoplastic syndromes such as erythroderma, leukocytoclastic vasculitis, and sweet syndrome; and rheumatological paraneoplastic syndromes such as paraneoplastic pemphigus and polymyalgia rheumatica (12). Sweet syndrome is an acute febrile neutrophilic dermatosis characterized by Acute onset of tender, erythematous nodules, papules, plaques, or pustules on extremities, face, or upper trunk along with fever, malaise, and neutrophilia. Approximately 20% of patients with Sweet syndrome have underlying hematologic malignancy (13). In this review, we have tried to identify case reports in which there is an association between MG and MPN. These cases have been compared and contrasted to evaluate whether MG can occur as a PNS in patients with underlying MPN.

Materials and Methods

A systematic review of case reports was conducted by searching PubMed, Scopus, and Google scholar using the following keywords, (a) 'Myasthenia Gravis' + 'Chronic Myeloid Leukemia,' (b) 'Myasthenia Gravis' + 'Polycythemia Vera,' (c) 'Myasthenia Gravis' + 'Essential Thrombocythemia,' (d) 'Myasthenia Gravis' + 'Primary/ Pre-fibrotic Myelofibrosis' and (e) 'Myasthenia Gravis' + 'Myeloproliferative neoplasms/ diseases.' Articles other than case reports and case series were removed. All case reports of the association of myasthenia gravis with myeloproliferative neoplasms were identified. Cases of MPNs with non-neurological paraneoplastic syndromes were excluded. A Comparative study between the cases was done to identify the chronological order of events and know whether Myasthenia gravis can be considered a possible neurological paraneoplastic syndrome in patients with myeloproliferative neoplasms.

Results

A total of 13 cases of MPNs associated with MG were identified. Twelve of them were males and only one female. The median age was 49 years (Inter-Quartile Range = 35.5 – 64.5). The first case was reported in 1961 and the latest one in 2020. Nine patients had moderate to massive splenomegaly, while physical examination findings were not mentioned in the other 4. The most common type of MPN associated with MG was CML (10 out of 13 patients). 2 patients had PV, and 1 had PMF. There were no cases of ET associated with MG. In most of the patients (8 out of 13), MG symptoms appeared after a diagnosis of MPN was made. Two patients had MG preceding the MPN, and three had them simultaneously. In patients diagnosed first with MG, the MPN was diagnosed after an average of 8 years, whereas in patients diagnosed with MPN initially, the onset of MG was after a few months. 77% (10/13) of the patients had either anti-AChR or anti-MuSK antibodies positive. All patients with simultaneous presentation of both MPN and MG had either positive anti-AChR or anti-MuSK antibodies. Most patients were treated with steroids and

Table 1. Comparison of all currently available case reports of association between myeloproliferative neoplasms (MPNs) and myasthenia gravis (MG).

No. and Author	Age/ Sex	Type of MPN	Type of praneoplastic disease	Chronological order of clinical events	JAK2 Mutation	Thymoma	Splenomegaly	AChR/MuSK antibodies
1. Sasi S et al., 2020. (15)	57/ F	PV	MG	Simultaneous presentation	+ve	No	Yes, 18 cm	AChR negative, MuSK positive
2. Sasi S et al., 2020. (15)	63/ M	PV	MG	PV treated with hydroxyurea for 6 months, complicated with pancytopenia. MG diagnosed after 6 months of treatment with hydroxyurea	+ve	No	Yes, 15.4 cm	AChR +ve
3. Kopp C R et al., 2019. (16)	40/ M	CML	Ocular MG (oMG)	CML chronic phase → Treated with imatinib 400 mg daily → Complete hematologic response after 3 weeks → oMG after 4 months	Not known	Yes	Not known	AChR +ve
4. Sanford D et al., 214. (17)	40/ M	CML	MG	CML → Treated with Nilotinib 300 mg oral BID → Hematologic remission after 3 months → Generalised MG diagnosed after 6 months of treatment with Nilotinib	Not known	No	Yes,	AChR +ve
5. Sharma N et al., 2012. (18)	34/ M	CML	MG	Simultaneous presentation	Not known	Not known	Not known	AChR +ve High titre
6. Kumar P et al., 2007. (19)	47/ M	CML	oMG	Simultaneous presentation	Not known	No	Yes, 6 cm	AChR +ve
7. Pavithran K et al., 2002. (20)	25/ M	CML	MG	MG without thymoma treated with thymectomy. CML diagnosed 68 months after thymectomy	Not known	No	Yes, 14 cm	No
8. Altomare G et al., 1996. (21)	71/ M	PMF	MG	IMF (untreated) → MG	Not Known	Yes	Yes	AChR +ve
9. Pérez A et al., 1995 (22)	66/ M	CML	MG	CML → Treated with Interferon alpha 2a, 9 MU daily → Complete hematologic response after 6 months and interferon stopped → MG presents after 9 months	Not known	No	Not known	AChR +ve

(Continued)

Table 1. Comparison of all currently available case reports of association between myeloproliferative neoplasms (MPNs) and myasthenia gravis (MG). (*Continued*)

No. and Author	Age/ Sex	Type of MPN	Type of praneoplastic disease	Chronological order of clinical events	JAK2 Mutation	Thymoma	Splenomegaly	AChR/MuSK antibodies
10. Shimoda k et al., 1994. (23)	37/M	CML	MG	CML → ASCT → Chronic GVHD → MG presents after 49 months of transplantation	Not known	No	Yes	AChR +ve
11. Wanders et al., 1981. (24)	51/M	CML	MG	MG treated with thymectomy followed by 6 – Mercaptopurine. CML was diagnosed after 12.5 years of treatment with 6-MP	Not known	Radiologically – No Pathologically – Yes	Not mentioned	Yes (Antibodies against skeletal muscle and epithelioid thymus cells were present in high titres)
12. Wohl M A et al., 1972 (25)	32/M	CML	Eaton-Lambert Myasthenic syndrome	CML treated with Busulfan which was stopped after 5 months because of bone marrow aplasia. MG was diagnosed 1 year after stopping Busulfan	Not known	No	Yes, Massive	No
13. Djaldeiti M et al., 1961. (26)	70/ M	CML	MG	CML treated with Busulfan for 4 years, stopped due to generalized weakness. MG was diagnosed 2 months after CML was stopped by Tensilon test	Not known	Yes, Radiologically	Yes, 6 cm	No

cholinergic agents for MG. Five of them underwent thymectomy, out of which only four had radiologically or pathologically proven thymoma. All patients had satisfactory remission of MG symptoms.

Among eight patients in whom MG occurred after treatment initiation for MPN, 6 had CML, and one each had PV and IMF. Two of them were treated with tyrosine kinase inhibitors (TKI) and two with busulfan; one each Hydroxyurea, interferon-alpha 2a, and autologous stem cell transplantation (ASCT). The case of PMF was untreated. The earliest reports were of 2 CML patients who

developed MG after several years of treatment with busulfan. A summary of all cases of MPNs associated with MG is presented in tables 1 and 2 (14-25).

Discussion

PNS are mainly autoimmune. When the body tries to eliminate tumor cells, it launches an immune response, targeting normal neural tissues (11). This could be mediated by antibodies or by T-cells.

Table 2. Treatments and outcomes of all currently available case reports of association between myeloproliferative neoplasms (MPNs) and myasthenia gravis (MG).

No.	Treatment for MG	Treatment for MPN	Outcome
1	Steroids + Azathioprine → Tacrolimus → Mycophenolate	Hydroxyurea	Remission from PV and MG
2	Pyridostigmine	Hydroxyurea	Remission from PV and MG
3	Neostigmine → Thymectomy	Imatinib (TKI)	MG → symptoms resolved, CML → Complete hematologic and partial molecular response
4	Pyridostigmine + Prednisolone	Nilotinib (TKI)	MG → symptoms resolved, CML → satisfactory response
5	Not mentioned	Not mentioned	Improved
6	Steroids and Pyridostigmine	Imatinib 400 mg daily (TKI)	Re-evaluation after 12 weeks showed regression of spleen with a complete hematological cytogenetic response. There was resolution of ptosis and ophthalmoplegia. AchR turned negative.
7	5 sessions of plasmapheresis → thymectomy → Steroids + Cholinergic	Hydroxyurea	He remained in the chronic phase during the last 6 months of follow up. His myasthenia symptoms remained stable.
8	Thymectomy → Prednisolone and Pyridostigmine	None	Follow-up bone marrow biopsies have been refused by the patient.
9	Not known	Interferon alpha 2a	MG → Not known CML → Complete hematologic response
10	Pyridostigmine + Immunosuppressive therapy	ASCT (from HLA identical sister)	Not mentioned
11	Initially started on pyridostigmine → Thymectomy after 1 month → Followed by 6-mercaptopurine + pyridostigmine	Busulfan after stopping 6-MP	Good response. Condition has remained satisfactory.
12	Neostigmine, Prednisolone	Busulfan followed by 6-Thioguanine	Electromyograph of August 1976 was within normal limits, and neostigmine was then stopped. He remained in haematological remission taking 6-thioguanine in August 1979.
13	Pyridostigmine 60 mg daily → Irradiation to thymic area → Thymectomy	Busulfan for 4 years	Remission from CML and MG

Antibodies targeted against an accessible membrane target is directly responsible for the disease, as in the case of acetylcholine receptor (AChR) antibodies in myasthenia gravis, P/Q type of voltage-gated calcium channels (VGCC) in Lambert Eaton Myasthenic syndrome (LEMS), and encephalitis associated with anti-NMDA receptor antibodies (10). It has been documented that tumor outcome is better among patients with paraneoplastic syndromes (10). Myasthenia gravis (MG) is a prototypical autoantibody-mediated disease. The autoantibodies in MG target structures within the neuromuscular junction (NMJ), thus affecting neuromuscular transmission. Immune mechanisms that describe both the B cell- and autoantibody-mediated pathogenesis by AChR and MuSK MG subtypes are highlighted in figures 1 and 2.

It begins with naïve B cells in the bone marrow, which encounter self-antigens and receive T cell help in the thymus. Then they differentiate into autoantibody specific memory B cells, which are activated into antibody-secreting short-lived plasma-blasts or antibody-secreting long-lived plasma cells, which reside in the bone marrow and may also be present in the thymus. AChR autoantibodies are of IgG1, and MuSK are of IgG4 subclasses. They then migrate to the neuromuscular junction (NMJ) and produce various clinical features of MG (4).

Traditionally, there are many described differences between MG of AChR and MuSK subtypes. AChR MG has IgG1 and IgG3 autoantibodies and is mostly associated with thymic hyperplasia. CD20 negative plasma cells are responsible for auto-antibody production.

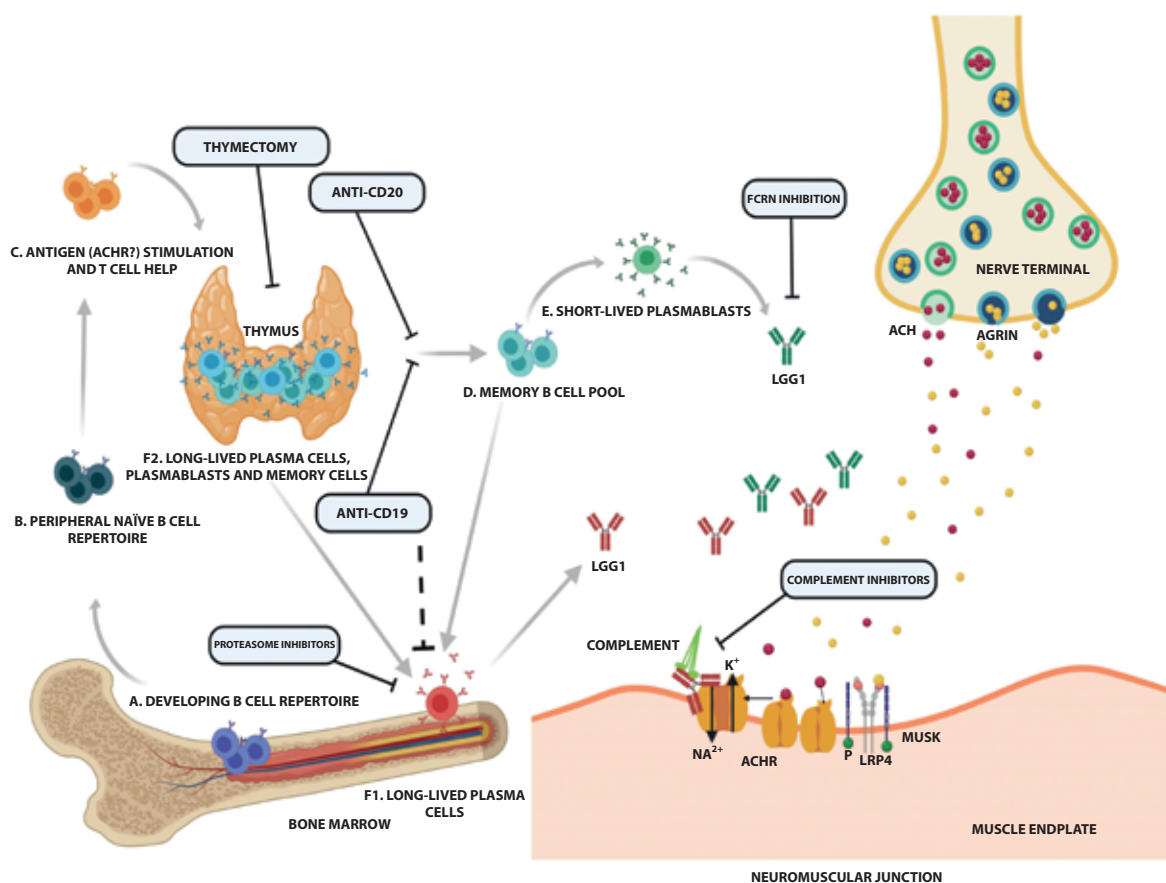


Figure 1. Immune mechanism for production of AChR antibodies in Myasthenia Gravis (The figure is reproduced with permission from: Fichtner ML, Jiang R, Bourke A, Nowak RJ, O'Connor KC. Autoimmune Pathology in Myasthenia Gravis Disease Subtypes Is Governed by Divergent Mechanisms of Immunopathology. *Front Immunol.* 2020;11:776. Published 2020 May 27. doi:10.3389/fimmu.2020.00776)

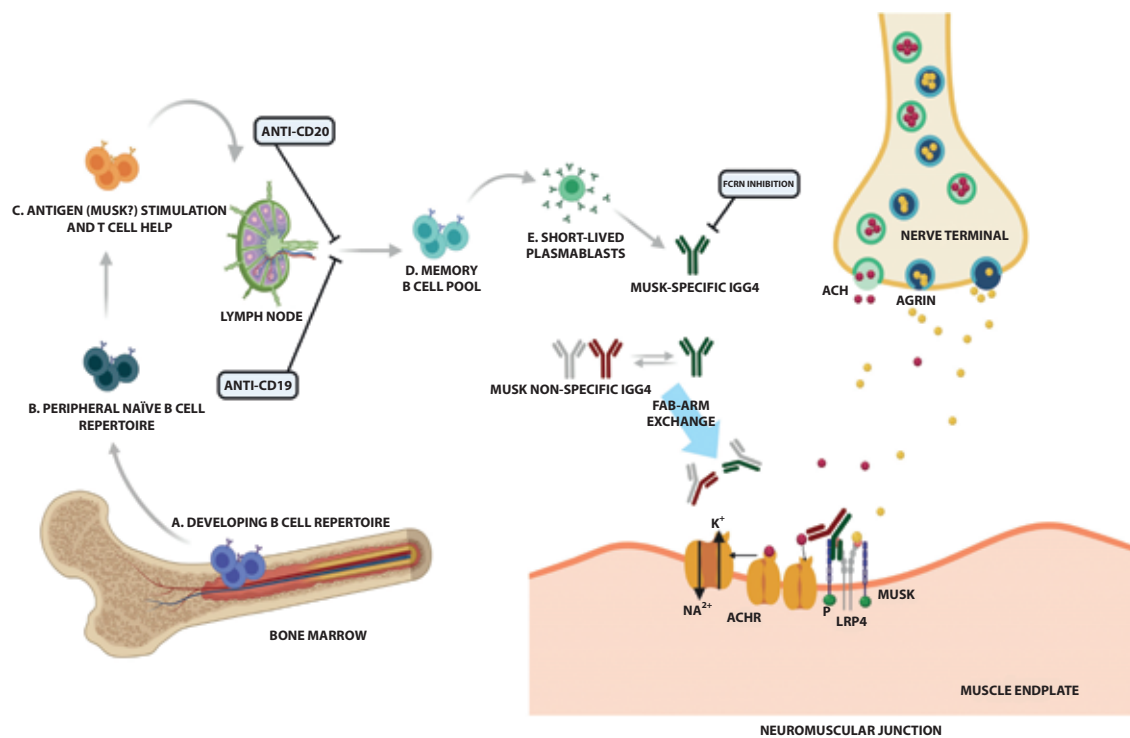


Figure 2. Immune mechanism for production of MuSK antibodies in Myasthenia Gravis (The figure is reproduced with permission from: Fichtner ML, Jiang R, Bourke A, Nowak RJ, O'Connor KC. Autoimmune Pathology in Myasthenia Gravis Disease Subtypes Is Governed by Divergent Mechanisms of Immunopathology. *Front Immunol.* 2020;11:776. Published 2020 May 27. doi:10.3389/fimmu.2020.00776)

In contrast, MuSK MG has IgG4 autoantibodies and is less likely to be associated with thymoma. CD20 positive plasmablasts are seen in them. Hence, AChR MG has a better chance of responding to thymectomy, and the MuSK subtype has a better chance of responding to rituximab (4).

MG is a recognized paraneoplastic syndrome in patients with thymoma (~15% of MG patients) (7), secondary to AChR/MuSK antibodies' production from the thymic source. Only 31% had thymoma in our cohort, whereas 77% had positive AChR/ MuSK antibodies. In patients whose MG occurred after the diagnosis of MPN, it was considered secondary to the treatment. However, from figures 1 and 2, it is evident that alterations in bone marrow morphology can result in the production of AChR/MuSK antibodies causing MG. Considering that 10 out of the 13 patients in our cohort had positive auto-antibodies though only 4 of them had thymic hyperplasia, we hypothesize that

the bone marrow proliferation was responsible for the production of autoantibodies in these patients. The authors of many reports had associated the onset of MG symptoms with the use of drugs to treat MPNs, e.g.: TKI in (16-18), busulfan in (24-26), and interferon-alpha in (21). However, there is no clarity in the mechanism of drug-induced MG in these reports. We assume that MG occurs as a neurologic paraneoplastic syndrome due to AChR/ MuSK auto-antibodies produced from abnormal bone marrow, which act at the NMJ, in patients with MPNs.

Among BCR-ABL1 negative MPNs (PV, ET, and PMF), survival is the longest in ET (median estimated at 20 years) and shortest in PMF (median estimated at six years). In the last 15 years, many MPN specific, mutually exclusive mutations were identified, namely JAK2 (chromosome 9p24), CALR (chromosome 19p13.2), and MPL (chromosome 1p34). JAK2 is the most frequent mutation with 98% in PV, 50%

- 60% in ET, and 55%- 65% in PMF. CALR and MPL mutations are usually absent in PV but occur in ET and PMF. The frequency of CALR mutation in both ET and PMF is about 20%-25%. MPL mutations are the rarest of the three and occur in about 3% - 4% cases of ET and 6% - 7% cases of PMF (27).

Figure 3 is a flowchart showing the classification of MPNs based on chromosomal mutations. JAK2 and MPL mutations are believed to directly activate JAK-STAT and make myeloproliferation cytokine independent or hypersensitive.

The precise mechanism of mutant CALR-induced myeloproliferation is less clear, but mouse models have suggested a primary effect on platelet production (28). Targeted therapy with JAK inhibitors has so far failed to induce selective suppression of the disease clone in MPN (29). The primary aim of treatment in PV and ET is to prevent thrombosis and alleviate symptoms. Randomized trials have shown the antithrombotic value of twice-daily aspirin in PV (30, 31), hydroxyurea in high-risk ET (32), and phlebotomy (hematocrit

target <45%) in PV (33). Aspirin therapy has also been shown to alleviate microvascular symptoms, such as erythromelalgia and headaches effectively, and possibly prevent vascular events in JAK2-mutated ET (34). The only treatment in MF that can cure the disease or prolong survival is stem cell transplantation (SCT). As most patients with Philadelphia chromosome-negative MPNs have V617F mutation in Janus kinase 2 (JAK2), JAK inhibitor ruxolitinib is being used in myelofibrosis (MF) and hydroxyurea resistant or intolerant polycythemia vera (PV). However, there is no evidence that it reduces the malignant clone (measured by the allele frequency of JAK2 V617F in the bone marrow) or alters the natural history of PV (i.e., leukemic transformation, myelofibrosis).

Tyrosine Kinase Inhibitors (TKIs, E.g., Imatinib, Nilotinib, Dasatinib) are currently the mainstay of treatment in Philadelphia chromosome-negative MPNs. In the pre-Imatinib era, allogeneic stem cell transplantation was the therapy of choice for CML and remains the only proven curative treatment.

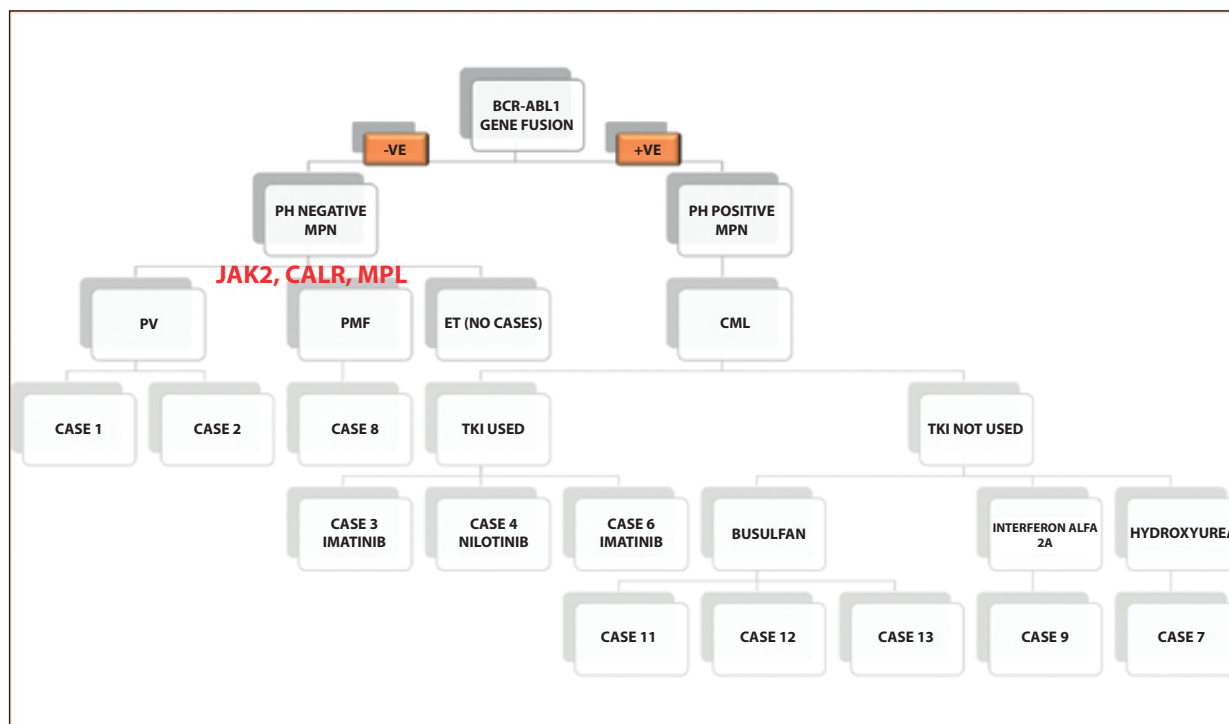


Figure 3. Flowchart showing the classification of Myeloproliferative Neoplasms based on chromosomal mutations.

IFN- α -based regimens were the pharmacologic treatment of choice in early phase CML (35). Adding pegylated IFN- α (peg-IFN- α) at a dose of 50 to 90 μ g weekly to imatinib resulted in statistically significant improvements in major metabolic response (MMR) and complete molecular remission (CMR) rates (36, 37). TKIs cannot eliminate quiescent CML stem cells despite virtually complete inhibition of BCR-ABL1 kinase activity (38). After TKI therapy initiation, BCR-ABL1 transcripts measured in blood or BM decline logarithmically but cannot be eliminated (39).

Conclusion

Considering that 10 out of the 13 patients in our cohort had positive auto-antibodies though only 4 of them had thymic hyperplasia, we hypothesize that the bone marrow proliferation was responsible for the production of autoantibodies in these patients. We assume that MG occurs as a neurologic paraneoplastic syndrome due to AChR/ MuSK auto-antibodies produced from abnormal bone marrow, which act at the NMJ, in patients with MPNs. As the clonal cell population cannot be eliminated entirely in the bone marrow even after treatment with tyrosine kinase inhibitors (TKI) in Ph +ve MPNs and JAK2 inhibitors in Ph -ve MPNS, MG can occur even in patients who are treated with these agents. A high index of suspicion is needed to diagnose it early, and treatment should be initiated immediately with steroids and anticholinergic agents.

Our group is studying the unmet clinical needs in Myeloproliferative neoplasms and CML like cost effective analysis for second generations TKIs when used as upfront [40], the association of tuberclosis with CML [41], the reactivation of hepatitis B with CML [42], ophthalmic manifestations as initial presentation in patients with CML [43], Effects of intermittent fasting on CML [44], autoimmune hemolytic anemia and its association with different therapies in CML [45], priapism [46,47], male fertility [48], obesity related surgeries in patients with CML [49,50] as well as effect of environmental life style on MPNs (51).

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Ethical Approval: Not required (literature review)

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