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...
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 | MG | 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. Djaldetti 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     | 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-secretting 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)
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 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%

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 paraneoplastic syndrome due to AChR/ MuSK auto-antibodies produced from abnormal bone marrow, which act at the NMJ, in patients with MPNs.

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**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)
- 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).

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 μg 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 tuberculosis 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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Not required (literature review)

### References

1. Robertson N. Enumerating neurology. Brain. 2000;123 (Pt 4):663-4.
2. Conti-Fine BM, Milani M, Kaminski HJ. Myasthenia gravis: past, present, and future. J Clin Invest. 2006;116:2843-54.
3. Phillips WD, Vincent A. Pathogenesis of myasthenia gravis: update on disease types, models, and mechanisms. F1000Res. 2016;5:F1000 Faculty Rev-1513 doi:10.12688/f1000research.8206.1.
4. 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 doi:10.3389/fimmu.2020.00776.
5. Sasi S, Yassin MA, Fadul AM. A Case of Acquired von Willebrand Disease Secondary to Myeloproliferative Neoplasm. Case Rep Oncol. 2020;13:733-7.
6. Barbui T, Thiele J, Gisslinger H, Kvasnicka HM, Vannucchi AM, Guglielmelli P, et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. Blood Cancer J. 2018;8(2):15. doi:10.1038/s41408-018-0054-y.
7. Yassin MA, Nehmeh SA, Nashwan AJ, Kohla SA, Mohamed SF, Ismail OM, et al. A study of 18F-FLT positron emission tomography/computed tomography imaging in cases of prefibrotic/early primary myelofibrosis and essential thrombocytemia. Medicine (Baltimore). 2020;99(45):e23088. doi:10.1097/MD.
8. Yassin MA, Taher A, Mathews V, Hou HA, Shamsi T, Tuğlular TF, et al MERGE: A Multinational, Multicenter Observational Registry for Myeloproliferative Neoplasms in Asia, including Middle East, Turkey, and Algeria. Cancer Med. 2020;9:4512-26.
9. Turkina A, Wang J, Mathews V, Saydam G, Jung CW, Al Hashmi HH, et al TARGET: a survey of real-world
management of chronic myeloid leukaemia across 33 countries. Br J Haematol. 2020;190:869–76.

10. Tefferi A, Pardanani A. Myeloproliferative Neoplasms: A Contemporary Review. JAMA Oncol. 2015;1:97–105.

11. Kannoth S. Paraneoplastic neurologic syndrome: A practical approach. Ann Indian Acad Neurol. 2012;15:6–12.

12. Pittocch SJ, Kryzer TJ, Lennon VA. Paraneoplastic antibodies-coexist and predict cancer, not neurological syndrome. Ann Neurol. 2004;56:715–9.

13. Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. Dosage error in article text. Mayo Clin Proc. 2010;85:838–54. [published correction appears in Mayo Clin Proc. 2011;86:364.

14. Cunha DG, Campos-do-Carmo G, Marujo JM, Verardino GC. Paraneoplastic Sweet’s syndrome. An Bras Dermatol. 2018;93:576–8.

15. Sasi S, Yassin MA, Kamran S, Mnatsakanyan V. Association of polycythemia vera with positive JAK2V617F mutation and myasthenia gravis: A report of two cases. Clin Case Rep. 2020;00:1–4. doi.org/10.1002/ccr3.3574.

16. Kopp CR, Jandial A, Mishra K, Sandal R, Malhotra P. Myasthenia gravis unmasked by imatinib. Br J Haematol. 2019 Feb;184(3):321. doi: 10.1111/bjh.15557.

17. Sanford D, MacDonald M, Nicolle M, Xenocostas A. Sweet’s syndrome in a man with myeloid leukemia treated by Busulfan. Blood 1968;32:336–40.

18. Verstovsek S, Kantarjian H, Mesa RA, Pardanani AD, Cortes-Franco J, Thomas DA, et al. Safety and efficacy of INCBO18424, a JAK1 and JAK2 inhibitor, in myelofibrosis. N Engl J Med. 2010;363:1117–27.

19. Rampal R, Al-Shahrour F, Abdel-Wahab O, Patel JP, Brunel JP, Mermel CH, et al. Integrated genomic analysis illustrates the central role of JAK-STAT pathway activation in myeloproliferative neoplasm pathogenesis. Blood. 2014;123:e123–33.

20. Tefferi A. JAK inhibitors for myeloproliferative neoplasms: clarifying facts from myths. Blood. 2012;119:2721–30.

21. Landolfi R, Marchioli R, Kutti J, Gisslinger H, Tognoni G, Patrono C, et al. European Collaboration on Low-Dose Aspirin in Polycythemia Vera Investigators. Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med. 2004;350:114–24.

22. Pascale S, Petrucci G, Dragani A, Habib A, Zaccardi F, Pagliaccia F, et al. Aspirin-insensitive thromboxane biosynthesis in essential thrombocytopenia is explained by accelerated renewal of the drug target. Blood. 2012;119:3595–603.

23. Cortelazzo S, Finazzi G, Ruggeri M, Vestri O, Galli M, Rodeghiero F, et al. Hydroxyurea for patients with essential thrombocytopenia and a high risk of thrombosis. N Engl J Med. 1995;332:1132–6.

24. Marchioli R, Finazzi G, Specchia G, Cacciola R, Cavazzina R, Cilloni D, et al. Cardiovascular events and intensity of treatment in polycythemia vera. N Engl J Med. 2013;368:22–33.

25. Alvarez-Larrán A, Cervantes F, Pereira A, Arellano-Rodrigo E, Pérez-Andreu V, Hernández-Boluda JC, et al. Observation versus antiplatelet therapy as primary prophylaxis of thrombosis in low-risk essential thrombocytemia. Blood. 2010;116:1205–10.

26. Ahmed W, Van Etten RA. Alternative approaches to eradicating the malignant clone in chronic myeloid leukemia: tyrosine-kinase inhibitor combinations and beyond. Hematology Am Soc Hematol Educ Program. 2013;2013:189–200.

27. Peudhomme C, Guilhot J, Nicolini FE, Guerri-Bresler A, Ridal-Huguet F, Maloisel F, et al. INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. Blood 1968;32:336–40.

28. Copland M, Hamilton A, Elrick LJ, Baird JW, Allan EK, Jordanides N, et al. Dasatinib (BMS-354825) targets an earlier progenitor population than imatinib in primary CML but does not eliminate the quiescent fraction. Blood. 2006;107:4532–9.

29. Roeder I, Horn M, Glauche I, Hochhaus A, Mueller MC, Loeffler M. Dynamic modeling of imatinib-treated chronic
myeloid leukemia: functional insights and clinical implications. Nat Med. 2006; 12:1181-4.

40. Adel A, Abushanab D, Hamad A, Abdulla M, Izham M, Yassin M. Assessment of Dasatinib Versus Nilotinib as Upfront Therapy for Chronic Phase of Chronic Myeloid Leukemia in Qatar: A Cost-Effectiveness Analysis. Cancer Control 2021;28:10732748211001796.

41. Iqbal P, Soliman A, De Sanctis V, Yassin MA. Association of tuberculosis in patients with chronic myeloid leukemia: a treatment proposal based on literature review. Expert Rev Hematol 2021;14:211-7.

42. Attaya A, Ahmad A, Daghestani D, Mushtaq K, Yassin MA. Evaluation of Hepatitis B Reactivation Among Patients With Chronic Myeloid Leukemia Treated With Tyrosine Kinase Inhibitors. Cancer Control 2020;27(1):1073274820976594.

43. Yassin MA, Ata F, Mohamed SF, et al. Ophthalmologic manifestations as the initial presentation of chronic myeloid leukemia: A Review. Surv Ophthalmol 2021:S0039-6257(21)00144-2.

44. Yassin MA, Ghasoub RS, Aldapt MB, et al. Effects of Intermittent Fasting on Response to Tyrosine Kinase Inhibitors (TKIs) in Patients With Chronic Myeloid Leukemia: An Outcome of European LeukemiaNet Project. Cancer Control 2021;28:10732748211009256.

45. Hamamyh T, Yassin MA. Autoimmune hemolytic anemia in chronic myeloid leukemia. Pharmacology 2020;105:630-8.

46. Ali E, Soliman A, De Sanctis V, Nussbaumer D, Yassin M. Priapism in Patients with Chronic Myeloid Leukemia (CML): A Systematic Review. Acta Biomed 2021;92(3):e2021193.

47. Ali EA, Nashwan AJ, Yassin MA. Essential thrombocythemia with (type2) calreticulin presented as stuttering priapism case report and review of literature. Clinical Case Reports 2021;9:399-404.

48. Yassin MA, Soliman AT, De Sanctis V. Effects of tyrosine kinase inhibitors on spermatogenesis and pituitary gonadal axis in males with chronic myeloid leukemia. J Cancer Res Ther 2014;2:116-21.

49. Yassin MA, Kassem N, Ghassoub R. How I treat obesity and obesity related surgery in patients with chronic myeloid leukemia: An outcome of an ELN project. Clin Case Rep 2021; 9:1228-34.

50. Abdulla MA, Chandra P, Akiki SE, Aldapt MB, Sardar S, Chapra A, Nashwan AJ, Sorio C, Tomasello L, Boni C, Yassin MA. Clinicopathological Variables and Outcome in Chronic Myeloid Leukemia Associated With BCR-ABL1 Transcript Type and Body Weight: An Outcome of European LeukemiaNet Project. Cancer Control. 2021 Aug 1;28:10732748211038429.

51. Allahverdi N, Yassin M, Ibrahim M. Environmental Factors, Lifestyle Risk Factors, and Host Characteristics Associated With Philadelphia Negative Myeloproliferative Neoplasm: A Systematic Review. Cancer Control. 2021 Jan-Dec;28:10732748211046802. doi: 10.1177/10732748211046802. PMID: 34645293; PMCID: PMC8521755.

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