CASE REPORT

Rare Pattern of Myelodysplastic Syndrome (MDS) with Serum Monoclonal Immunoglobulin: Case Report

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ABSTRACT

Background • Myelodysplastic syndromes (MDS) are clonal hematopoietic stem cell disorders characterized by bone marrow dysplasia, ineffective hematopoiesis, and cytopenias. Monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM) patients have a high risk of secondary MDS or acute myeloid leukemia (AML) compared to healthy persons, and chemotherapy or transplantation may result in secondary treatment-related MDS.

Methods • A patient was diagnosed with both MDS and MGUS, which was treated using thalidomide, dexamethasone, and danazol. A follow-up blood test was conducted to determine leukocyte and hemoglobin levels.

Results • Immunoprotein electrophoresis showed M protein peak with IgA+ κ components. Nuclear cells proliferated actively in bone marrow aspirates. Bone marrow analysis suggested a myelodysplastic syndrome with myeloblastoma (MDS-RS) and a new plasmacytoma. The immunophenotype was shown as follows: R5 cells (red) are about 15.5%. Among the CD38+CD45 cells, about 95.9% of cKappa cells and 1.7% of cLambda cells are considered as plasmacytoma. Gene detection showed that the patient carried 14 gene mutations, and karyotype analysis showed that they had normal male chromosome structure. The patient was diagnosed as MDS and MGUS, and finally discharged after treatment with thalidomide (75 mg daily), dexamethasone (3 mg daily), and danazol (200 mg twice daily). Within 1 year, the disease has stabilized.

Conclusion • The combination of plasma cell disease and myeloid malignancy may increase mortality. This is uncommon and may be easily misdiagnosed if not detected early. When a myeloid neoplasm tests positive for MDS and serum M protein, clinicians should evaluate for other plasma cell disease (*Altern Ther Health Med.* 2023;29(3):266-270).

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INTRODUCTION

Plasmacytoma, including monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM), is characterized by related damage to tissue and organ caused by a non-functional monoclonal antibody (M protein).[1,2] In recent years, the prevalence rate of plasma cell disease has increased gradually, and with continuous improvements in treatment, patient survival has improved. However, the risk of secondary myeloid diseases such as myeloid neoplasms including acute myeloid leukemia (AML) and myelodysplastic syndrome (MSD) has increased, which certainly increases the mortality of the disease. Myeloid tumor is characterized by cytopenia, myelodysplasia, and inefficient hematopoiesis,[3] which differ from plasmacytomas in terms of clinical and pathological characteristics. As a result, MM or MGUS seldom coexists with myeloid neoplasms. The combination of plasma cell illness and myeloid malignancies may increase mortality, which is presently uncommon, and there is no standardized treatment.

The coexistence of plasma cell disease and a myeloid tumor is still extremely unusual, with an incidence of about 0.3-1.1%.[4] The clinical reports on the subject are very few and there is no standardized therapy. The etiology and mechanism are unknown; however, they may be connected to clonal heterogeneity, the bone marrow microenvironment, and immunosuppression. Latency in diagnosis and treatment may be attributed to a lack of knowledge about the disease.[5]

In this report, we share one such case and offer a therapy used for reference to raise clinician awareness of this disease and emphasize the significance of early diagnosis and treatment.

Figure 1. Immunoprotein electrophoresis (a) M protein peak is visible; (b) The component is considered as IgA + kappa type.

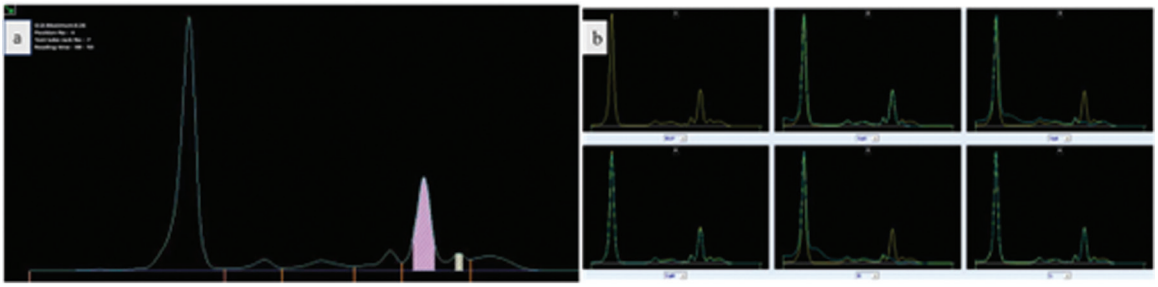
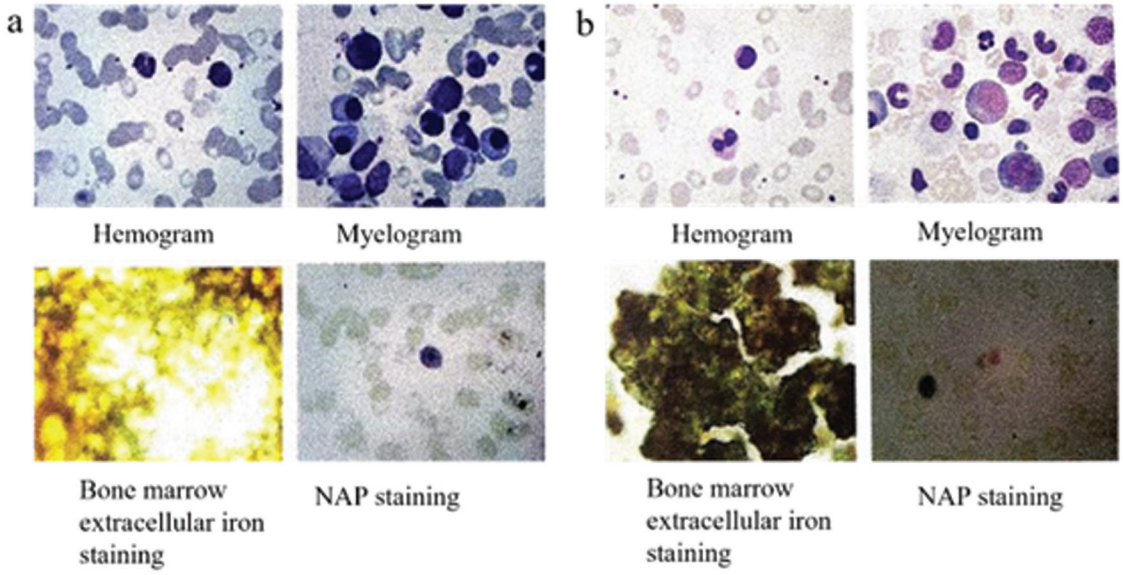


Figure 2. Bone marrow aspirate findings: (a) Nucleated cell proliferation was active, the proportion of plasma cells was high; (b) The results may be considered as myelodysplastic syndrome with sideroblast (MDS-RS) and plasmacytoma may be diagnosed.



Report of a case

The patient was a 70-year-old man who had been taken to the hospital for an abnormal hemogram. After admission, a regular blood test and bone marrow aspirate were carried out.

RESULTS

The expression of white blood cells and hemoglobin

The patient's regular blood test revealed that the level of white blood cells and hemoglobin was reduced. An M protein peak was apparent on immunoprotein electrophoresis, with an IgA+kappa component (Figure 1).

The active state of nuclear cell proliferation

Nucleated cell proliferation was active in the bone marrow aspirate. Sideroblasts accounted for 27% with a sideroblastic anemia myelogram. There was proliferation of three cell lines and a high number of plasma cells (8.5%) was observed. Megaloblastic anemia was not ruled out (Figure 2a). Bone marrow aspiration suggested that myelodysplastic syndrome with sideroblast (MDS-RS) and plasmacytoma may be present (Figure 2b).

Immunophenotype results

Immunophenotyping revealed the following: the R5 cells (red) were about 15.5% and there was a group of plasmacytes of about 5.6% in this region which expressed CD38, CD138, and CD56, while did not expressing CD19 or CD45. In the $CD38^{+}$ $CD45^{-}$cells, cKappa cells were about 95.9%, cLambda cells were about 1.7%, and the diagnosis was made for plasmacytoma (Figure 3).

Gene detection

Genetic testing revealed that the patient carried mutations in 14 genes (Table 1), and karyotype analysis showed that he had a normal male chromosome structure (Figure 4).

Diagnosis and treatment

The patient was diagnosed with both MDS and MGUS and was eventually released following the therapy with thalidomide (75 mg daily), dexamethasone (3 mg daily), and danazol (200 mg twice daily). In the past year, his condition has stabilized according to telephone follow-up.

Table1. Mutations in 14 genes

	Results	Implication	
		Drug	**Diagnosis/Prognosis**
Possible mutations	TP53 p.R248Q	MDS: lenalidomide (drug fast, A); MDS: decitabine (susceptive, D); AML: decitabine (susceptive, A); CLL: fludarabine or bendamustine (drug fast, A)	MDS: poor prognosis (A); AML: poor prognosis (A); MPN: poor prognosis (A); CLL/SLL: poor prognosis (A)
	IDH1 p.R132C	AML: ivosidenib (susceptive, A)	AML: poor prognosis (A); MDS: poor prognosis (C); PMF: poor prognosis (A); PV: poor prognosis (A)
	ASXL1 p.A640Gfs*14	--	MDS poor prognosis (C); MPN poor prognosis (A); CMML poor prognosis (A); AML poor prognosis (A)
	ASXL1 p.L1009Hfs*6		
	TET2 p.L226Wfs*24	MDS: HMAs (susceptive, A); MDS: azacytidine (susceptive, A)	
	TET2 p.Y1245Lfs*22		AML: poor prognosis (A)
	TET2 p.T1884A		
	TET2 p.Y1902C		
	TET2 p.C262_E263 delinsX		
	ZRSR2 c.203+1G>T	--	MDS: poor prognosis (C)
	ZRSR2 c.771+1G>A		
	ZRSR2 p.E133Gfs*11	--	MDS: poor prognosis (A)
	ZRSR2 p.L237*fs*1		
	SRSF2 p.R94_P95deli nsPL	--	CMML: poor prognosis (A) MPN: poor prognosis (A)
Genetic predisposition	--	--	
Quality of sample	qualified		

DISCUSSION

MM/MGUS is the primary diagnosis and AML/MDS is the secondary diagnosis.

Research has shown that there is a relationship between MM or MGUS with a second primary malignancy (SPM) along with treatment-related myeloid malignancies (T-MN). These malignancies are caused by multiple factors such as the disease itself, cytogenetics, host, environment, and treatment[6] (Figure 5).

Disease and cytogenetics

In comparison to the general population, individuals with MM/MGUS have an 11-fold greater chance of developing AML or MDS, particularly in IgA/IgG MGUS. There is a higher risk when the M protein is greater than 1.5 g/L, which is determined by the heterogeneity of the disease itself and cytogenetics represented by complex karyotype (CK) and gene mutations. The most common cytogenetic abnormalities include chromosomes 5 and 7. The molecular abnormalities identified included mutations of several genes such as TP53, JAK2V617F, RAS, FLT3-ITD, and NPM1.[7] AML/MDS usually develop 4 years following a diagnosis of MM/MGUS.

Furthermore, since MGUS and MM take longer to diagnose, the chance of subsequent illnesses including MDS, myeloid leukemia, and non-Hodgkin's lymphoma is higher. The patient carried 14 mutations in genes including TP53, IDH1, TET2, and ZRSR2 which increased his risk of developing SPM and T-MN.

Treatment factors

According to previous studies, hematopoietic stem cell transplantation (HSCT) and medications such as lenalidomide, melphalan, and cyclophosphamide may promote the tendency of SPM and T-MN after treatment, The longer the drug usage period, the greater the risk of MDS and acute leukemia.[8-10]

Figure 3. Immunophenotyping: Pattern was consistent with plasmacytoma.

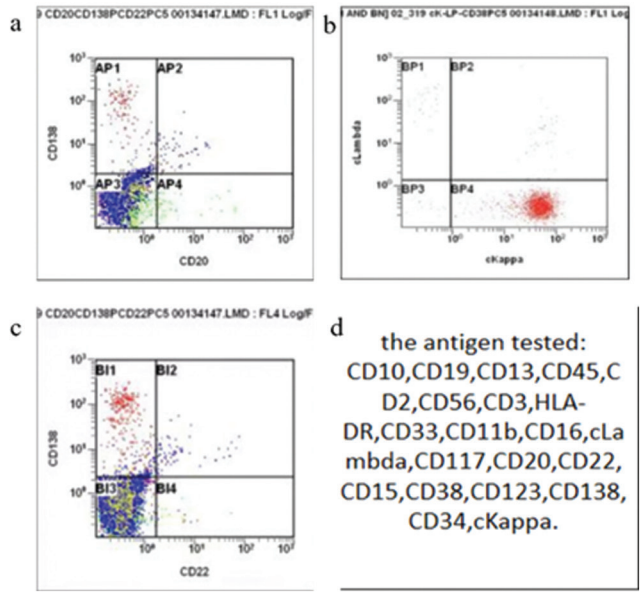


Figure 4. Normal male chromosome structure.

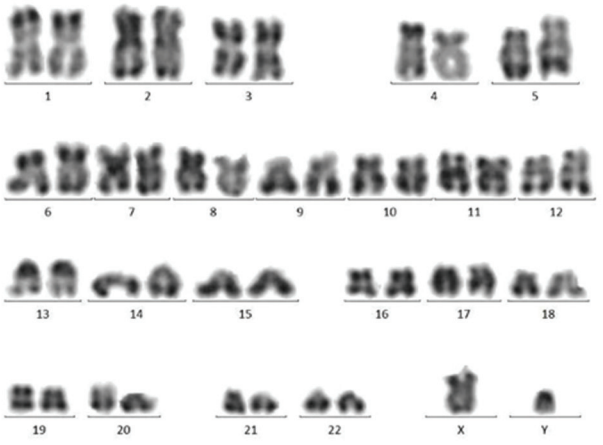
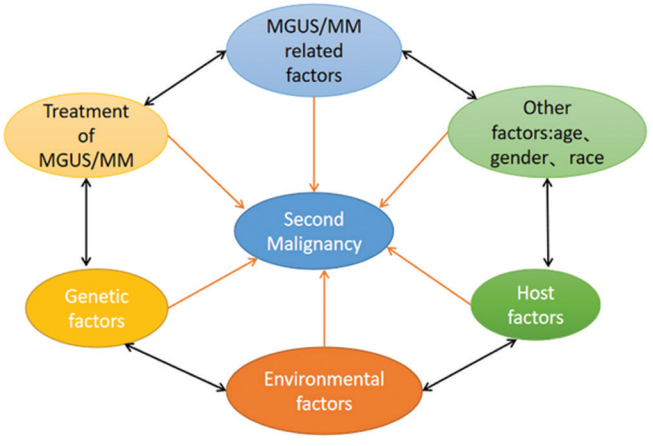


Figure 5. Proposed model of second malignancies after MM/MGUS



Medication

At present, multiple drugs including proteasome inhibitors, immunomodulators, and monoclonal antibodies have played an important role in the treatment of hematological disease. It is found that lenalidomide, melphalan, and cyclophosphamide are linked to a high risk of SPM and T-MN after MM or MGUS.

Lenalidomide is an immune modifier that is most commonly used in treatment of MM. Research showed that MM/MGUS patients who have been treated with lenalidomide have a higher risk of SPM than those without lenalidomide. Although characterized by rapid positive effect and fewer side effects compared to thalidomide and pomalidomide, lenalidomide is more likely to cause SPM. Melphalan and cyclophosphamide are anti-tumor drugs and they both increase the risk of SPM and T-MN after MM or MGUS. Although not currently commonly used to treatment of MM, previous studies have shown that melphalan is more likely to promote AML than cyclophosphamide, and the longer the melphalan is used, the greater the risk.

Hematopoietic Stem Cell Transplantation (HSCT)

It is well known that HSCT is an important way to prolong the life of patients with hemopathy. According to research on HSCT, patients who received HSCT were at greater risk of developing AML or MDS than those without HSCT, which is related to a high dose of drug before HSCT. Without chemotherapy, there was no significant difference in the incidence of AML or MDS before and after HSCT.

Other factors

In addition, age, sex, race, and obesity may all have an impact on the development of SPM and T-MN. Older men are more likely to develop AML and MDS after MM or MGUS.[11]

From this, we may conclude that MGUS and MM patients have a higher risk for secondary MDS or AML than healthy persons and that chemotherapy or transplantation may result in secondary treatment related MDS. This implies that, regardless of therapy, patients with MM/MGUS have an inherent risk of developing secondary myeloid malignancies. Consequently, MDS alterations in MGUS or MM patients may be due to the illness itself, rather than MDS coexistence.

Six individuals with lymphocytic lymphoma (LPL) problems were identified in another investigation of 1198 MDS patients. LPL is a kind of lymphoma that is distinct from other B lymphocyte proliferative diseases. Waldenström macroglobulinemia (WM) is identified when LPL infiltrates the bone marrow and has serum monoclonal immunoglobulin M. Most patients with LPL/WM are positive for MYD88L265P mutations as a rare complication of MDS, which aids in the diagnosis of suspected LPL/WM.[12,13] Because LPL has no distinct morphology, immunophenotype, or genetic alterations, it is a one-of-a-kind diagnosis that should be arrived at based on both clinical manifestations and pathology. Although LPL/WM may be identified by a bone marrow test if lymphadenectasis is evident, a lymph-node

biopsy should be done to rule out other kinds of lymphoma. The fact that MDS patients have a 2%–10% risk of combining MGUS shows that LPL might be an intermediate step between MDS and MGUS, and physicians should look for MDS patients who have concurrent LPL/WM.

The 70-year-old man in this case was diagnosed with both MDS and MGUS. For this patient with mutations in 14 genes, there was a higher risk of developing MDS before chemotherapy. With serum monoclonal IgM immunoglobulin, a high proportion of plasma cells in bone marrow, and no significant lymphadenectasis on physical examination, this patient was not subjected to MYD88 gene mutation analysis, so it is possible for him to have a potential LPL and increase the risk of MDS combined with MGUS.

Treatment

Since there is no effective treatment for this disease, a combination of proteasome inhibitors, immunomodulators, and monoclonal antibodies is more appropriate.[14,15]

According to a few published cases, therapy with thalidomide, dexamethasone, and danazol has achieved a good therapeutic effect. As a synthetic androgen, danazol is helpful for hematopoiesis and serves as adjuvant therapy in MDS. Thalidomide, an immunomodulator, is commonly used to treat MDS and plasmacyte disease for its anticancer effect, antiangiogenetic action, and regulation of the immune system. Our experience has shown that it is at lower risk of leading to SPM and T-MN compared to lenalidomide. The combination of thalidomide and dexamethasone will not only relieve symptoms of MDS but possibly delay the progression of MGUS to MM.[16,17] Although the combination of these three drugs provides a new way to treat this disease, allogeneic stem cell transplantation should be initiated as early as possible (Table 2).

It should be emphasized that a positive serum non-functional monoclonal antibody (M protein) is an essential marker for plasma cell disorders, that the level of serum M protein is critical for determining effectiveness, and that serum M protein persistence after therapy suggests treatment failure. To measure therapeutic response and anticipate treatment success, serum protein electrophoresis should be performed regularly both during and after treatment[18].

CONCLUSIONS

Although the above studies can provide a reasonable explanation for the phenomenon of simultaneous diagnosis of plasmacytoma with myeloid tumor, the coexistence of such double hematological tumors is still clinically rare, with few reports, unknown mechanisms, difficult therapy, and an uncertain prognosis. The current work contributes to the growing body of evidence that MDS and MGUS are produced from two distinct clones and that their coexistence is the consequence of a disrupted bone marrow niche. It might be a new disease with distinct clinical and molecular features as well as a poor prognosis. The current treatments remain nonstandard without a uniform protocol. In the future, we will continue to explore effective treatment to improve the prognosis of patients with coexistence of multiple malignancies.

Table 2. A comparison of effect between Lenalidomide, Melphalan, and Cyclophosphamide

Drug	Essence	Function
Thalidomide	Immunomodulator	Immunoregulation Anti-inflammatory action Anti-angiogenesis Sedative and analgesic
Dexamethasone	Glucocorticoid	Immunosuppression Anti-inflammatory action Anti-anaphylaxis Anti-rheumatism
Danazol	Synthetic androgen	Hematopoiesis Androgenic action

FUNDING

This work was supported by Yunnan Applied Basic Research Projects-Joint fund for applied basic research of Kunming Medical University, Yunnan Provincial Department of Science and Technology [No.2018FE001 (-113)]; the Open project of Yunnan clinical medical center (No. 2020LCZXKF-XY02); and Yunnan health training project of high-level talents (No. D-2018018).

AUTHOR CONTRIBUTION

Yating Lin and Jun He contributed equally to the work.

CONFLICT OF INTEREST

None

REFERENCES

1. Kanzaki G, Okabayashi Y, Nagahama K, et al. Monoclonal Immunoglobulin Deposition Disease and Related Diseases. *J Nippon Med Sch*. 2019;86(1):2-9. doi:10.1272/jnms.JNMS.2019_86-1
2. Westhrin M, Kovcic V, Zhang Z, et al. Monoclonal immunoglobulins promote bone loss in multiple myeloma. *Blood*. 2020;136(23):2656-2666. doi:10.1182/blood.2020006045
3. Menssen AJ, Walter MJ. Genetics of progression from MDS to secondary leukemia. *Blood*. 2020;136(1):50-60. doi:10.1182/blood.2019000942
4. Bouchla A, Thomopoulos T, Papageorgiou S, et al. Coexistence of Myeloid and Lymphoid Neoplasms: A Single-Center Experience. *Adv Hematol*. 2019;2019:1486476. doi:10.1155/2019/1486476
5. Mouhieddine TH, Weeks LD, Ghobrial IM. Monoclonal gammopathy of undetermined significance. *Blood*. 2019;133(23):2484-2494. doi:10.1182/blood.2019846782
6. Roeker LE, Larson DR, Kyle RA, Kumar S, Dispenzieri A, Rajkumar SV. Risk of acute leukemia and myelodysplastic syndromes in patients with monoclonal gammopathy of undetermined significance (MGUS): a population-based study of 17 315 patients. *Leukemia*. 2013;27(6):1391-1393. doi:10.1038/leu.2013.34
7. Pemmaraju N, Shah D, Kantarjian H, et al. Characteristics and outcomes of patients with multiple myeloma who develop therapy-related myelodysplastic syndrome, chronic myelomonocytic leukemia, or acute myeloid leukemia. *Clin Lymphoma Myeloma Leuk*. 2015;15(2):110-114. doi:10.1016/j.clml.2014.07.001
8. Nadiminti K, Sidiqi MH, Meleveedu K, et al. Characteristics and outcomes of therapy-related myeloid neoplasms following autologous stem cell transplantation for multiple myeloma. *Blood Cancer J*. 2021;11(3):63. doi:10.1038/s41408-021-00454-y
9. Jonsdottir G, Björkholm M, Turesson I, et al. Cumulative exposure to melphalan chemotherapy and subsequent risk of developing acute myeloid leukemia and myelodysplastic syndromes in patients with multiple myeloma. *Eur J Haematol*. 2021;107(2):275-282. doi:10.1111/ejh.13650
10. Poh C, Keegan T, Rosenberg AS. Second primary malignancies in multiple myeloma: A review. *Blood Rev*. 2021;46:100757. doi:10.1016/j.blre.2020.100757
11. Castillo JJ, Gertz MA. Secondary malignancies in patients with multiple myeloma, Waldenström macroglobulinemia and monoclonal gammopathy of undetermined significance. *Leuk Lymphoma*. 2017;58(4):773-780. doi:10.1080/10428194.2016.1217527
12. Pemmaraju N, Shah D, Kantarjian H, et al. Characteristics and outcomes of patients with multiple myeloma who develop therapy-related myelodysplastic syndrome, chronic myelomonocytic leukemia, or acute myeloid leukemia. *Clin Lymphoma Myeloma Leuk*. 2015;15(2):110-114. doi:10.1016/j.clml.2014.07.001
13. Zagaria A, Coccaro N, Tota G, et al. Myelodysplastic syndrome with 5q deletion following IgM monoclonal gammopathy, showing gene mutation MYD88 L265P. *Blood Cells Mol Dis*. 2015;54(1):51-52. doi:10.1016/j.bcmd.2014.07.022
14. Motomura Y, Umezawa Y, Arimatsu T, Okada K, Miura O, Kumagai T. Successful treatment with bortezomib for refractory fever associated with myelodysplastic syndrome with underlying lymphoplasmacytic lymphoma. *Clin Case Rep*. 2022;10(2):e05372. doi:10.1002/ccr3.5372
15. Yan W, Qu XY, Li H, et al. Coexistence of plasma cell neoplasia and myelodysplastic syndrome with excess blasts: case reports and literature review. *Ann Palliat Med*. 2021;10(12):12431-12440. doi:10.21037/apm-21-3210
16. Klimkowska M, Nannya Y, Gran C, et al. Absence of a common founder mutation in patients with cooccurring myelodysplastic syndrome and plasma cell disorder. *Blood*. 2021;137(9):1260-1263. doi:10.1182/blood.2020007555
17. Chang WI, Koh HK, Yoon SS, Kim HS, Eom KY, Kim IH. The predictive value of serum myeloma protein in solitary plasmacytoma. *Radiat Oncol J*. 2020;38(2):129-137. doi:10.3857/roj.2019.00570
18. Quintini M, Arniani S, Ascani S, et al. Identification of two independent clones underlying the co-existence of myelodysplastic syndrome with excess of blasts type 2 and isolated 5q- and smouldering multiple myeloma. *Cytopathology*. 2020;31(1):59-62. doi:10.1111/cyt.12752