Observational Study

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Proactive consultation of laboratory medicine increased diagnostic rate of multiple myeloma

One single center's 12-year experience

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Abstract

Multiple myeloma (MM) was one of the hardest cancers to diagnose because of numerous nonspecific symptoms, leading to diagnostic delay. Proactive consultation of laboratory medicine (PCLM) could help timely diagnosis of blood cancers, avoiding diagnostic delay. This study aimed to evaluate the effect of PCLM on diagnosis and outcomes in MM. This retrospective study was conducted in newly diagnosed MM patients from 2011 to 2022. Implementation of PCLM initiated in 2015 with a laboratory-oriented algorithm. The annual diagnostic rate, patient demographics, the time intervals from symptom onset to diagnosis and to treatment, and clinical outcomes were analyzed. A total of 134 patients were newly diagnosed during the study interval. The diagnostic rate increased from 4.65 ± 1.59 to 7.43 ± 1.52 per million patient-visits after implementation of PCLM. The median time interval from symptom onset to diagnosis was significantly shortened after implementation of PCLM (50 days with interquartile range [IQR]: 24–136 days vs 150 days with IQR: 41–385 days, $P = .003$). Besides, the 1-year survival was significantly higher in patients diagnosed as MM after implementation of PCLM (72.4% vs 51.7%, $P = .035$). Implementation of PCLM not only increased diagnostic rate of MM and improved outcomes, but also raise awareness for MM and promote multidisciplinary collaboration in healthcare.

Abbreviations: COVID-19 = coronavirus disease-19, FEMH = Far Eastern Memorial Hospital, Ig = immunoglobulin, IQR = interquartile range, ISS = international staging system, MM = multiple myeloma, PCLM = proactive consultation of laboratory medicine.

Keywords: immunoparesis, interval from symptom onset to diagnosis, multiple myeloma, proactive consultation of laboratory medicine, rouleaux formation

1. Introduction

For decades, multiple myeloma (MM) has been considered as one of the hardest malignancies for diagnosis. The entire rarity and nonspecific symptoms of MM make it difficult to suspect this disease at the first time, hence leading to a diagnostic delay. In the UK, the proportion of MM was about 2% in newly diagnosed cancer patients every year.[1] In Taiwan, it was reported that MM accounted for approximately 0.6% of total new cases diagnosed as cancer.[2] Patients with MM could present with nonspecific symptoms, including low back pain, bone pain, dizziness, fatigue and so on.[3] Some MM cases could be accidentally found with emergency presentation such as repeated infection, renal dysfunction or compression fracture.[4,5] For patients who had co-morbidities that could mask MM-related symptoms, a prolonged diagnostic process was more likely to be experienced[6] and was usually associated with increased complications and worse outcomes.[7,8] Therefore, timely diagnosis should improve the outcome in patients with MM.

C-CC and J-LH have contributed to this study equally.

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

The study was approved by the Ethics Committee of Far Eastern Memorial Hospital (approval date: December 28, 2023 and approval number: 112228-E). The requirement for written informed consent was waived due to the retrospective nature of the study and the use of de-identified data. All procedures used in this study adhere to the tenets of the Declaration of Helsinki.

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The concept of proactive consultation of laboratory medicine (PCLM) was first issued by Dr Minoru Kuwajima.[9,10] In PCLM, patient-oriented laboratory comments would be reported on selected abnormal results of laboratory testing in each patient. Liaison service was also performed to remind the medical staff in primary care of further laboratory investigation and referral to specialist for diagnostic and therapeutic strategies. It was also reported that PCLM could help diagnosis and treatment in hematological malignancies.[11] In our hospital, PCLM has been performed especially in certain blood cancers since 2015. Hence, we aimed to survey whether PCLM help diagnosis of MM and improved the outcome as well.

2. Methods

2.1. Study design and data collection

A before-and-after study was designed to evaluate the diagnostic rate of MM in Far Eastern Memorial Hospital (FEMH), New Taipei, Taiwan. We retrospectively analyzed the clinical data of 134 consecutive patients who visited our outpatient department and emergency department and were newly diagnosed as MM in FEMH between 2011 and 2022. All enrolled patients must meet the international myeloma working group criteria for diagnosing MM.[12,13] In brief, MM was diagnosed based on the presence of clonal bone marrow plasma cells of 10% and more, accompanied with MM-defining CRAB features (hypercalcemia, renal failure, anemia and bone lesions). For those who had no CRAB features, MM could also be diagnosed with the presence of: clonal bone marrow plasma cells of 60% and more; serum free light chain ratio of 100 and higher, provided that the involved free light chain concentration is of 100 mg/L and higher; or more than one focal lesion that is of 5 mm and greater in size on magnetic resonance imaging. The international staging system (ISS) for MM, determined mainly by serum albumin and beta-2-microglobulin, was recorded in all enrolled patients. The documented dates for symptom onset, diagnosis, treatment and expiration were also collected to calculate the time intervals from symptom onset to diagnosis and to treatment, respectively. The date for symptom onset was recorded when patients' chief complaint was described and should be complied to the documented symptoms in the NICE referral guidelines.[14] Patients who had no symptoms mentioned in the NICE referral guidelines or whose symptoms were not well documented in the medical record were excluded from the analysis of intervals from symptom onset to diagnosis and to treatment. The date for diagnosis was recorded when the pathological report of bone marrow biopsy was documented; and the date for treatment was recorded when the patient initiated bortezomib or thalidomide therapy. The date for expiration was recorded when the patient expired or discharged due to terminal stage. One-year survival was then evaluated from treatment to expiration. This study was approved by the FEMH institutional review board (112228-E), which waived the requirement for patient informed consent.

2.2. Proposed algorithm

A proposed algorithm of PCLM in MM diagnosis in FEMH has been executed since 2015 (Fig. 1). Briefly, when a reversed albumin-to-globulin ratio (A/G reverse) was observed, proactive examination on peripheral blood smear would be reviewed to evaluate whether there was rouleaux formation of red cells; and vice versa. When both A/G reverse and rouleaux formation of red cells were observed, serum protein electrophoresis with immunosubtraction as well as referral to hematologist would be suggested for further investigation. Besides, when immunoparesis (i.e., one or more of uninvolved immunoglobulins (Igs) such as IgG, IgA and/or IgM below the lower limit of laboratory referenced range) was observed, serum protein electrophoresis with immunosubtraction as well as referral to hematologist would be recommended for further investigation. Furthermore, urine protein electrophoresis with immunofixation would also be suggested if immunoparesis of IgG, IgA, and IgM was found. The laboratory comment, including laboratory findings and suggestions, would be reported in patients who had not been diagnosed as MM before.

2.3. Statistical analysis

Statistical analysis was performed using SPSS software (version 19.0; SPSS, Inc, Chicago), Continuous variables were presented as mean with standard deviation or median with

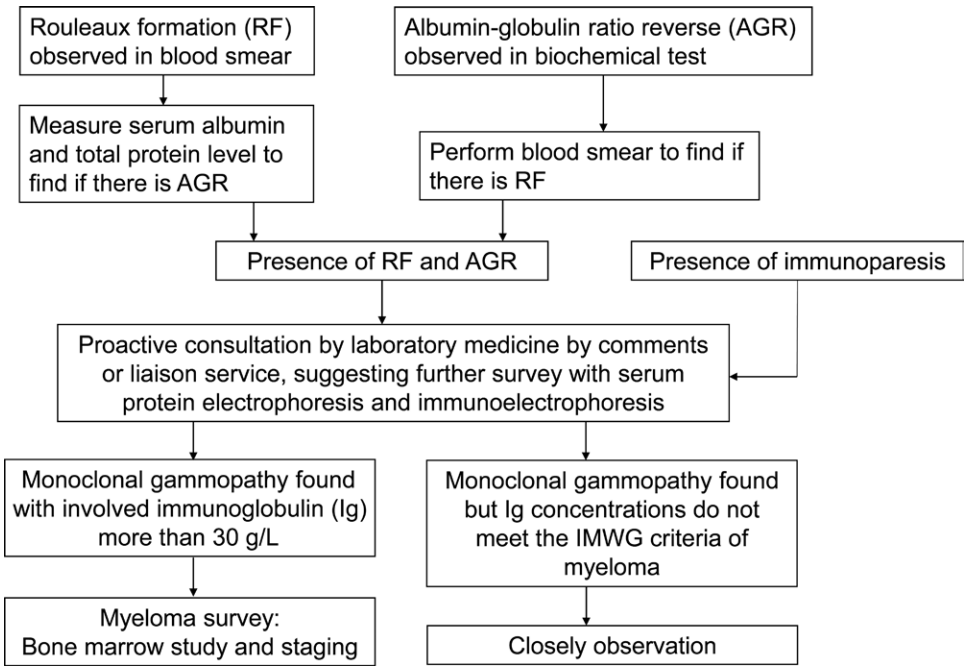

Figure 1. A proposed algorithm of PCLM in MM survey and diagnosis. MM = multiple myeloma, PCLM = proactive consultation of laboratory medicine.

interquartile range (IQR) as appropriate. Categorical variables were presented as counts and percentage; and Chi-square test was performed with Pearson's correlation or Fisher's exact test as appropriate. A *P* value less than .05 would be considered statistically significant.

3. Results

A total of 134 newly diagnosed MM patients were included between 2011 and 2022 in FEMH, where the annual patient-visits ranged from 1.46 to 1.94 million in outpatient department and emergency department. Before implementation of PCLM (from 2011 to 2014), 29 were newly diagnosed as MM and the annual incidence of newly diagnosed MM ranged from 3.18 to 7.34 per million patient-visits (Fig. 2). And 105 were newly diagnosed as MM after clinical execution of PCLM (from 2015 to 2022), of which 68 were diagnosed with the help of PCLM. The annual incidence of newly diagnosed MM ranged from 5.14 to 9.81 per million patient-visits after implementation of PCLM.

The demographic data and immunophenotype of MM patients were shown in Table 1. There was no significant difference of age, sex, and ISS between MM patients who were diagnosed before and after execution of PCLM. In our study population, 17 were excluded from evaluation of the interval from symptom onset to diagnosis as there was no specific symptoms or symptoms were not well documented in the medical record. And 4 additional patients were excluded from evaluation of the interval from symptom onset to treatment as they did not receive treatment finally. Both the intervals from symptom onset to diagnosis and to treatment were significantly shortened after execution of PCLM when compared with those before (the interval from symptom onset to diagnosis: 50 days [IQR: 24–136 days] vs 150 days [IQR: 41–385 days], $P = .003$; the interval from symptom onset to treatment: 62 days [IQR: 34–144 days] vs 200 [IQR: 64–209 days], $P = .004$). The 1-year survival was significantly higher in patients diagnosed as MM after execution of PCLM when compared with that before (72.4% vs 51.7%, $P = .035$). The most common immunophenotype of MM patients was IgG kappa (31.3%, n = 42), followed by IgG lambda (18.7%, n = 25), IgA lambda (14.9%, n = 20), IgA kappa (11.9%, n = 16), free light chain lambda (n = 14) and free light chain kappa (10.4%, n = 13) in our study population.

To summarize, an increasing trend had been shown in the diagnostic rate of MM since implementation of PCLM. Besides, the 1-year survival was significantly increased in patients diagnosed as MM after PCLM implementation. The intervals from symptom onset to diagnosis and to treatment were also significantly shortened after PCLM implementation, but there was no remarkable change in diagnosing MM in the early ISS with PCLM.

4. Discussions

In this study, we proved that the proposed algorithm of PCLM in MM diagnosis was clinically feasible and could help in increasing the diagnostic rate. Furthermore, it seemed that implementation of PCLM was associated with improved outcomes in 1-year survival and shortened time intervals from symptom onset to diagnosis and to treatment, but was not associated with diagnosing MM in the early ISS.

In most circumstances of malignancies, the presented symptoms could be indicative of the disease. Individual symptoms of MM were not predictive as those were commonly seen and usually nonspecific in clinical practice,[15] however, leading to diagnostic delay. Accumulating evidence demonstrated that diagnostic delay was considered to increase complications and to worsen the survival rate in MM;[7,16] and prompt diagnosis of MM may contribute to improved outcomes as well as quality of life.[8] Unfortunately, there were still some barriers to timely detection of MM in the real world, which could be multidimensional, including those related to disease characteristics, patients, clinical practitioners and health care systems. In the literature review, the median time interval from symptom onset to MM diagnosis was reported to be 163 days with IQR of 84 to 306 days in the UK[4] and was 99 days with IQR of 27 to 252 days in the US.[5] In comparison, the time interval (150 days, IQR: 41–385 days) before PCLM implementation in our study was similar with these findings. After implementation of PCLM, the median time interval from symptom onset to MM diagnosis was significantly shortened by approximately 3 months; and 1-year survival was also significantly increased in our study population. PCLM should play a vital role in avoiding diagnostic delay, subsequently increasing MM survival and reducing complications.

Recent studies revealed that MM could be more indicative with combination of individual symptoms and laboratory

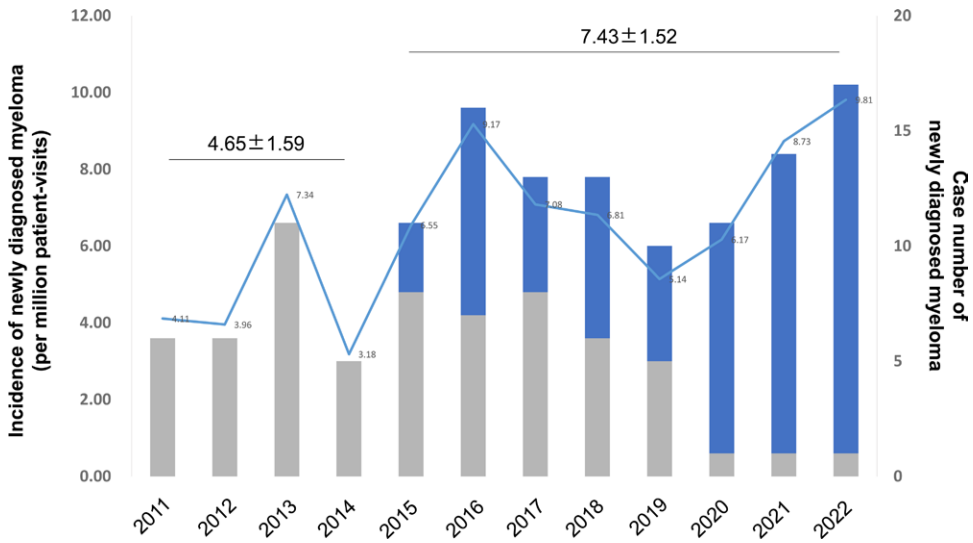

Figure 2. The annual incidence and case number of newly diagnosed MM before and after implementation of PCLM. The blue bar indicated the cases with MM diagnosis helped by PCLM. MM = multiple myeloma, PCLM = proactive consultation of laboratory medicine.

Table 1

Demographic data and immunophenotype of patients with MM in FEMH during 2011–2022.

Variables	Before PCLM (2011–2015)	After PCLM (2015–2022)			*P* value
		With PCLM	Without PCLM	*P* value	
MM case number	29	68	37		
Age	64 (57–75)	71 (60–78)	68 (60–73)	.472	.379
F/M	13/16	24/44	14/23	.791	.396
ISS					
1	3	9	11	.040	.405
2	15	12	19	<.001	.026
3	11	47	7	<.001	.198
Symptoms onset to diagnosis (d)	150 (41–385)	44 (24–132)	67 (30–165)	.280	.003
Symptoms onset to treatment (d)	200 (64–209)	55 (26–144)	71 (44–165)	.276	.004
Immunophenotype					
IgG kappa	13	21	8	.310	.077
IgG lambda	2	18	5	.146	.066
IgA kappa	1	7	8	.146	.192
IgA lambda	5	13	2	.079	.769
Free light chain kappa	3	3	7	.031	1.000
Free light chain lambda	4	4	6	.160	.734
IgM kappa	0	1	0	N/A	N/A
IgM lambda	0	1	0	N/A	N/A
Non-secretory	1	0	1	N/A	N/A
1-year survival	51.7%	67.6%	81.1%	.142	.035

Data were expressed as median with interquartile range (IQR).

Patients who had no symptoms mentioned in the NICE referral guidelines or whose symptoms were not well documented in the medical record were excluded from the analysis of intervals from symptoms onset to diagnosis and to treatment.

MM = multiple myeloma, N/A = not available, PCLM = proactive consultation of laboratory medicine.

investigation. It was reported that MM diagnosis could be strongly suggested by certain symptoms such as backache, fracture, joint or bone pain when coupled with laboratory abnormalities such as hypercalcemia and leucopenia.[15] It was also reported that increased plasma viscosity and erythrocyte sedimentation rate (ESR) could be useful in suggestion of MM diagnosis.[17] In contrast, we provided an algorithm of PCLM in MM diagnosis using observation of rouleaux formation of red cells in peripheral blood smear and blood test of total protein, albumin, Igs and protein electrophoresis with immunosubtraction to find if there were A/G reverse, immunoparesis and monoclonal gammopathy. High suspicion of MM and referral to hematologist would be recommended in the presence of laboratory abnormalities mentioned above. Additionally, 2 cases were primarily found as their blood specimens were somewhat difficult to be separated by centrifugation, implying the high plasma viscosity. Proactive blood test was then performed according to our algorithm of PCLM; and these patients were then referred to hematologist for further investigation. The final diagnoses in these 2 patients were IgA kappa MM, ISS 3 and IgA lambda MM, ISS 1, respectively. In the previous case reports of MM, it was also shown that hyperviscosity could be occasionally found, particularly in IgA MM.[18,19] Though plasma viscosity was not presented as one of the evaluation step in our proposed algorithm due to its rarity, laboratory staff should be aware of MM and initiate proactive laboratory investigation if there was failure in blood sample centrifugation or aspiration.

Though the proposed algorithm of PCLM in MM diagnosis seemed to be basically laboratory-oriented in our study, PCLM could actually play an integrated role in promoting multidisciplinary teamwork for medical care of MM. It was reported that lack of communication between different departments could be associated with diagnostic delay in blood cancers.[20] In perspective of this, PCLM could be one of potential solutions to address such challenges. Furthermore, it seemed that more clinical practitioners in primary care not only prescribed proper laboratory test but also consult hematologist timely in the clinical scenarios that MM should be ruled out from the differential diagnosis after implementation of PCLM. PCLM was shown to be a demonstration in clinical practice for multidisciplinary collaboration in diagnostic establishment and patient care of MM in our experience.

The outbreak of coronavirus disease-19 (COVID-19) occurred in May 2021 in Taiwan,[21] profoundly affecting the efficacy of healthcare system and changing the health-providing practice.[22–25] Fortunately, the outbreak was controlled with a series of prompt responses and interventions. During the COVID-19 pandemic, the healthcare system was overwhelmed with strained medical resources by a great many patients who required intensive care; and laboratory staff experienced exhaustion with a huge number of specimens for nucleic acid amplification and rapid antigen tests against severe acute respiratory syndrome coronavirus 2. It was also reported that the COVID-19 pandemic had a negative impact on the health-seeking behavior of patients, leading to declines in both outpatients and hospitalizations.[26,27] Despite of these dilemma, the diagnostic rate of MM during the COVID-19 pandemic was seemingly consistent throughout the period after PCLM implementation in our study. The model of PCLM not only demonstrated the healthcare resilience but also assured the quality of medical care and laboratory survey.

The major limitations in our study included the retrospective study design focusing on MM and the limited case number in single medical center. Whether PCLM should have led to diagnosis of smoldering MM and monoclonal gammopathy of undetermined significance remained unknown. There were also other potential biases that could ambiguously contribute to the increase of the case number after implementation of PCLM from 2015 in our study, such as the updated diagnostic criteria for MM in 2014 by international myeloma working group or the expansion of referral facilities. Besides, we used ISS, rather than revised ISS for MM staging because of lack of cytogenetic analysis in our study population such as TP53 deletion, 1q21 gain, 1p32 deletion and so on. The following period was also not sufficient so only the one-year survival was analyzed. A large retrospective multicenter cohort study was warranted. Furthermore, only the time interval from symptom onset to diagnosis was collected and analyzed in our study,

rather than the interval from first presentation to diagnosis,[28] since the help-seeking route varied by country and territory. In the national health service system in the UK, people requesting help would be evaluated by the general practitioner in the community-based primary healthcare. They could then be referred to the specialist for further assessment. Alternatively, people could request specialists' help as the primary care on a walk-in basis in Taiwan, making it somewhat difficult to clearly define the date of first presentation to primary care and the subsequent analysis of time intervals.

5. Conclusion

In conclusion, the provided algorithm of PCLM could help MM diagnosis. Implementation of PCLM was associated with improved outcomes in 1-year survival and shortened time intervals from symptom onset to diagnosis and to treatment, but was not associated with diagnosing MM in the early ISS. Importantly, implementation of PCLM not only increased diagnostic rate of MM but also raise awareness for MM in the medical staff and promote multidisciplinary collaboration in healthcare.

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