

# Simultaneous multiple myeloma and non-small cell lung carcinoma: A case report and review of the literature

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**Abstract.** Multiple myeloma (MM) is the second commonest hematologic malignancy. Synchronous presentation of MM and lung cancer is a rare occurrence. The present study reports a case of MM combined with lung cancer and reviews previously reported cases of the co-existence of non-small cell lung carcinoma and MM. At Hebei General Hospital (Shijiazhuang, China), a 52-year-old man was diagnosed with MM complicated by lung lesion. Lung computed tomography (CT) showed an increase in lesion density after the second cycle of chemotherapy. The lesion was surgically removed and the patient was diagnosed with non-small cell lung carcinoma by lung biopsy pathology. After the fifth cycle of VDT (bortezomib, dexamethasone and thalidomide), the patient received autologous stem cell transplantation. Immunohistochemical staining for CD38, CD138, CD39, CD203a and TNF- $\alpha$  were positive in both MM and lung cancer; CD73 was only positive in lung cancer. The present study described the rare event of the simultaneous occurrence of MM and lung adenocarcinoma and discussed the potential link between the two tumors. CD38 may play a role in MM and lung cancer by changing the bone marrow microenvironment through adenosine.

## Introduction

Multiple myeloma (MM) is characterized by an excessive accumulation of plasma cells in the bone marrow. The diagnosis of MM requires monoclonal immunoglobulin and bone marrow examination or biopsy evidence (1). CD38 and CD138 are expressed by plasma cells in myeloma (2). Studies

have found that FGF-R3 and CD138 regulate autocrine and paracrine signals in MM and osteoprotegerin (OPG) has a role in myeloma bone disease through the receptor activator of nuclear factor- $\kappa$ B (RANK) ligand/RANK/OPG system (3-5). In addition to alkylating agents and corticosteroids, a number of new drugs have been used to treat MM in recent years. For example, thalidomide, bortezomib and daratumumab belong to immunomodulator proteasome inhibitors and monoclonal antibodies to CD38 are used for MM treatment (1,6). The etiology of MM remains to be elucidated.

Non-small cell lung carcinoma (NSCLC) accounts for ~80-85% of all carcinomas of the lungs (7). The pathogenesis of lung cancer remains to be elucidated. EGFR is a common gene mutation in NSCLC. However, drug treatment of NSCLC often leads to drug resistance through the acquisition of the EGFR T790M mutation in the later stage (8,9). Hematopoietic and solid cancers have effects on the function of T cells (10). Sporadic cases of the co-existence of MM and NSCLC have been reported. Patients with co-existing MM and lung cancer have a poor prognosis (11) and a standard treatment for these patients is lacking. However, the link between MM and NSCLC remains to be elucidated.

The present study described a case of MM that was diagnosed with NSCLC. The findings help expand the awareness of MM combined with NSCLC and provide a reference for strategies for early diagnosis and treatment.

## Case report

A 52-year-old man was treated in a local hospital because of lower limb pain, swelling and weakness for more than half a year. He developed sore limbs and weakness in the last two months and was transferred to Hebei General Hospital (Shijiazhuang, China) in August 2018. Detailed physical examination information was collected: Body temperature 36.5°C, pulse 80/min, respiration 20/min, blood pressure 126/86 mmHg, clear consciousness, normal skin color, no damage to mucosa and no swelling of spleen, liver or lymph nodes. The laboratory results at admission are presented in Table I. The levels of blood immunoglobulin (Ig) A, IgG and IgM were lower than normal (Fig. 1). Bence-Jones protein

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was positive. Bone marrow biopsy confirmed myeloma-like cells and immunostaining revealed positive staining for CD38, CD138, CD39, CD203a, TNF- $\alpha$ , CD6, CD7, MPO, CD3, CD20 and PAS and negative staining for CD34, CD73 and pan-cytokeratin (Fig. 2). The Lambda involvement/Kappa non-involved light chain ratio was >100. Hematuria immunofixation by electrophoresis, blood free light chain quantitative and urine free light chain results are shown in Table I. Several tumor markers were normal. Lung computed tomography (CT) images showed ground glass shadow in the upper lobe of the right lung (Fig. 3A). Multi-Disciplinary Treatment analysis suggested that the lung lesions were more likely to be malignant tumors, but the patient's family disagreed with the operation. Dynamic lung CT evaluation was performed. In addition, Radionuclide Bone Scans was performed (Fig. 4). Based on the laboratory results, the patient was diagnosed as MM (IgD- $\lambda$  type).

The patient was treated with VDT (bortezomib 1.3 mg/m<sup>2</sup> day 1 (D1), 4, 8, 11; dexamethasone 20 mg ivgtt D1, 2, 4, 5, 8, 9, 11 and 12) and thalidomide (100 mg oral qd). After one cycle, there was no significant change in lung CT. After the second cycle of treatment, lung CT showed that the density of ground glass shadow increased, with a size of 22x16x12 mm (Fig. 3B). The patient received surgery and was diagnosed with stage IA lung adenocarcinoma by thoracoscopic right pulmonary nodule resection without chemotherapy and radiotherapy (Fig. 5). At the same time, tumor markers were monitored (Table II). After the fifth cycle of VDT, the patient underwent autologous stem cell transplantation and was rechecked regularly in the outpatient department.

At the time of writing, the patient showed a beneficial therapeutic response to VDT and autologous stem cell transplantation. After the lung lesions were resected, no invasion was found at the cut edge of the tissue and no recurrence and new lesions were found in postoperative dynamic lung CT evaluation. Lung tumor markers were stable. No evidence of the lung cancer was detected.

## Discussion

MM is a genetically complex hematopoiesis malignancy, comprising 10% of all hematological malignancies (12). MM occurs alone as well as simultaneously or secondary with other tumors, such as lung cancer. When suffering from lung cancer and MM, the chronological occurrence of the two cancers needs to be clarified. Fewer than 20 cases of MM with lung cancer have been reported so far; four of these cases were lung adenocarcinoma cases and MM and lung cancer occurred simultaneously in only two cases (11,13-20). Zuo *et al* (17) reported a rare case of simultaneous MM and pulmonary adenocarcinoma; the patient was treated with bortezomib and is stable. The patient in the present study received thalidomide and was stable. It was hypothesized that MM and lung cancer appeared at the same time in the current case. From the comprehensive examination of laboratory, CT, whole-body bone scanning, immunohistochemistry and tumor marker analyses, it was possible to clearly diagnose MM. Prior to the diagnosis of MM, the lung CT showed ground glass shadow. At two months following MM treatment, CT evaluation of the lung revealed changes of the lesions; the lung lesions

Table I. Laboratory results at admission.

Item	Units	Value	Normal range/limit
<b>Biochemical indicators</b>			
Serum total protein	g/l	56.1↓	65-85
Serum albumin	g/l	34.9↓	40-55
Albumin	g/l	32.5↓	40-55
Globulins	g/l	20.30	20-40
Serum urea	mmol/l	4.59	2.5-7.1
Creatinine	mmol/l	66.48	53-132
Uric acid	$\mu$ mol/l	311.68	208-428
Lactic dehydrogenase	IU/l	164.6	120-250
Potassium	mmol/l	4.4	3.5-5.3
Calcium	mmol/l	2.36	2.11-2.52
<b>Complete blood count</b>			
Hemoglobin	g/l	98.00↓	130-175
White blood cell	10 <sup>9</sup> /l	5.18	3.5-9.5
Platelets	10 <sup>9</sup> /l	196.00	125-350
Erythrocyte sedimentation rate	mm/h	28↑	0-15
<b>Immunofixation electrophoresis</b>			
IgD- $\lambda$ type M protein		Positive	Negative
Urine protein qualitative		Positive	Negative
<b>Blood free light chain quantitative</b>			
Free light chain $\lambda$	mg/l	3,650	6-26
Kappa/lambda		0.0018	0.26-1.65
<b>Urine free light chain quantitation</b>			
Free light chain $\lambda$	mg/l	>3,675	<5
Kappa/lambda		<0.0035	

↑, Denotes above the upper limit of the reference range; ↓, denotes below the lower limit of the reference range.

were removed by surgery and the pathological diagnosis was stage IA lung adenocarcinoma without any lesions found in other organs; thus, it was assumed that none of the cancers were caused by metastasis of the other. In a case reported by Marinopoulos *et al* (20) MM was found 11 months after chemotherapy for lung cancer. Lin *et al* (15) report a case of MM diagnosed with lung cancer 18 months after treatment. The patient in the present study underwent systemic examination at admission and no lesions were found in other locations. The probability of lung tumor after only two months of chemotherapy is very low.

The pathological mechanisms of MM with lung cancer remain unclear. EGFR gene mutation is detected in the majority of solid tumors and also observed in MM cells (12,21). Studies have found that MM acquires resistance to EGFR inhibitor via induction of the pentose phosphate pathway (22-24). Dasatinib, a tyrosine kinase inhibitor, has been shown to

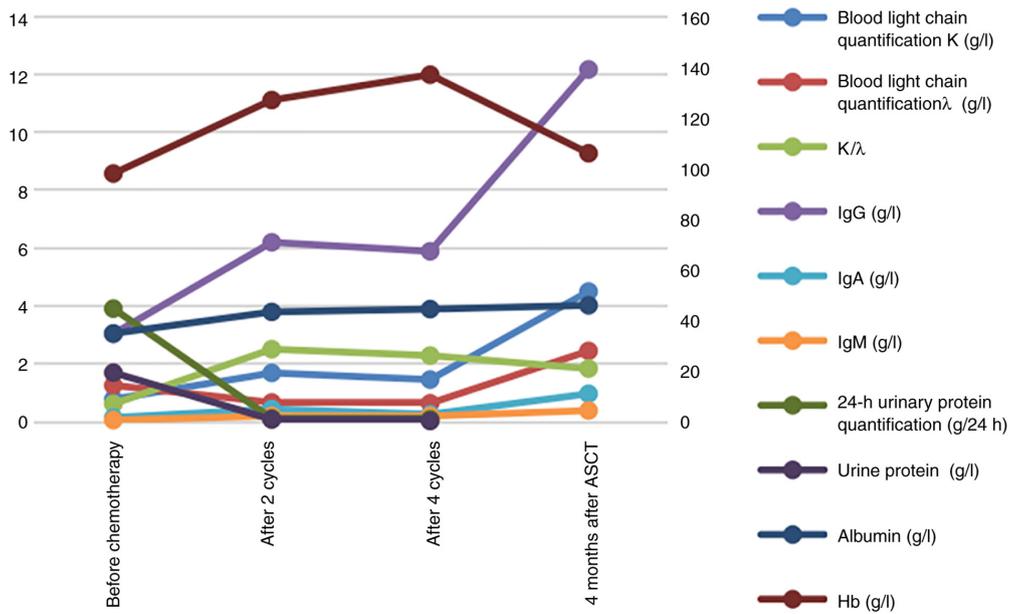


Figure 1. Changes of laboratory indicators. The series of blood light chain quantification ( $\kappa$ ,  $\lambda$  and  $\kappa/\lambda$ ), IgG, IgA and IgM, 24-h-urinary protein quantification and urine protein are drawn on the primary axis and the series of albumin and Hb are drawn on the secondary axis. Ig, immunoglobulin; Hb, hemoglobin.

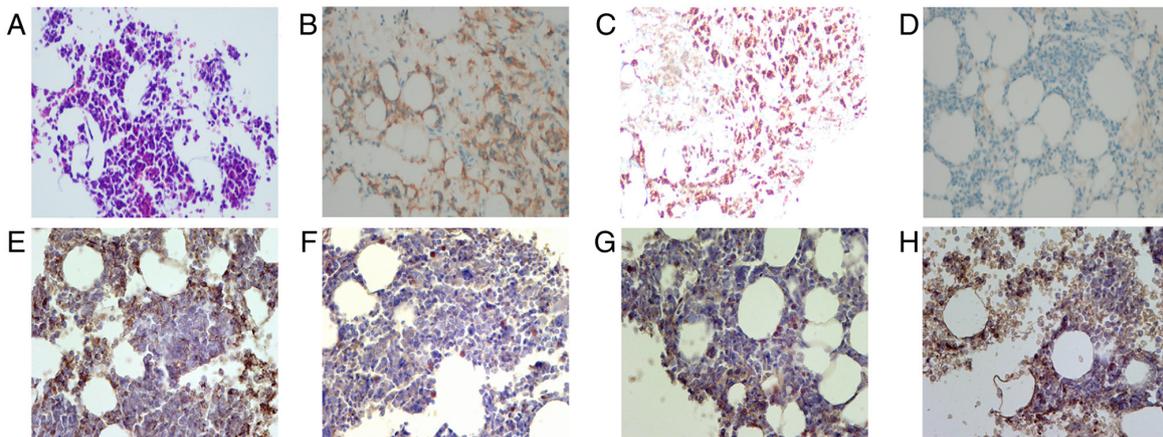


Figure 2. Immunostaining of bone marrow biopsy specimen for cytokines. (A) Hematoxylin and eosin (magnification, x200). (B)  $\lambda$  light chain positive (magnification, x200). (C) CD38 positive (magnification, x200). (D)  $\kappa$  light chain negative (magnification, x200). (E) CD39 positive (magnification, x400). (F) CD73 negative (magnification, x400). (G) CD203a positive (magnification, x400). (H) TNF- $\alpha$  positive (magnification, x400).

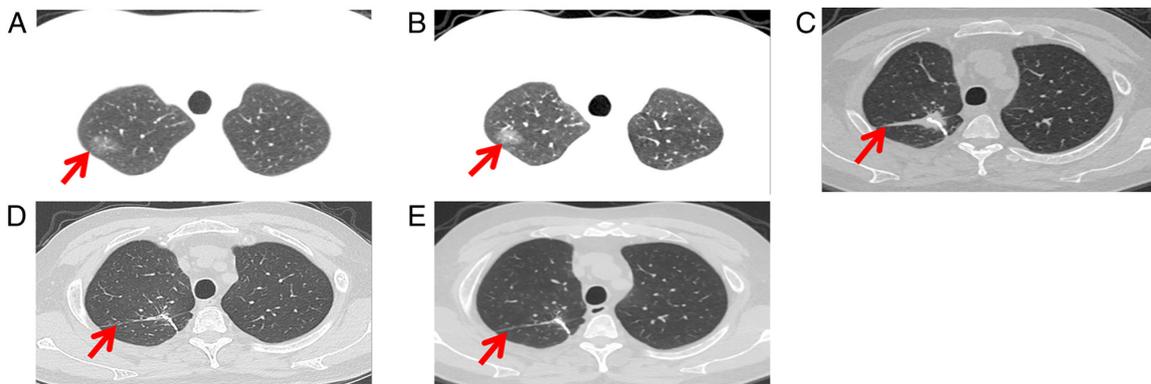


Figure 3. Images of computed tomography (red arrows indicate the lesions). (A-B) Preoperative computed tomography. (C-E) Imaging of postoperative pulmonary lesions. (A) Computed tomography on admission, the lesion was in the upper lobe of the right lung and its diameter was ~20 mm. (B) After two cycles of VDT, the shadow density of ground glass increased and its size was ~22x16x12 mm. (C) Three months after operation, the lesion site exhibited a strip sign (post-operative inflammatory reaction). (D) There were no new lesions in the lung one year after the operation. (E) At three years after the operation, there were no signs of recurrence.

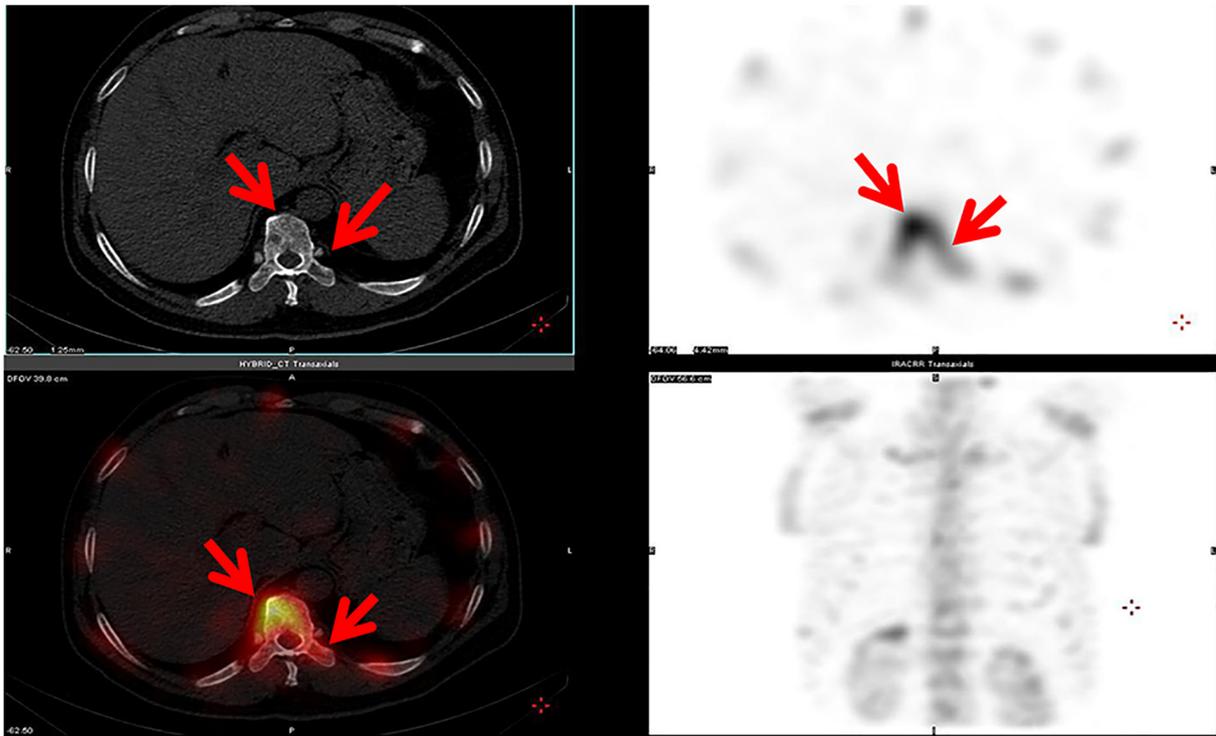


Figure 4. Radionuclide bone scans (red arrows showed the lesions). Radionuclide bone scans showed radio heightening shadows of the 10th thoracic vertebra and its left transverse process.

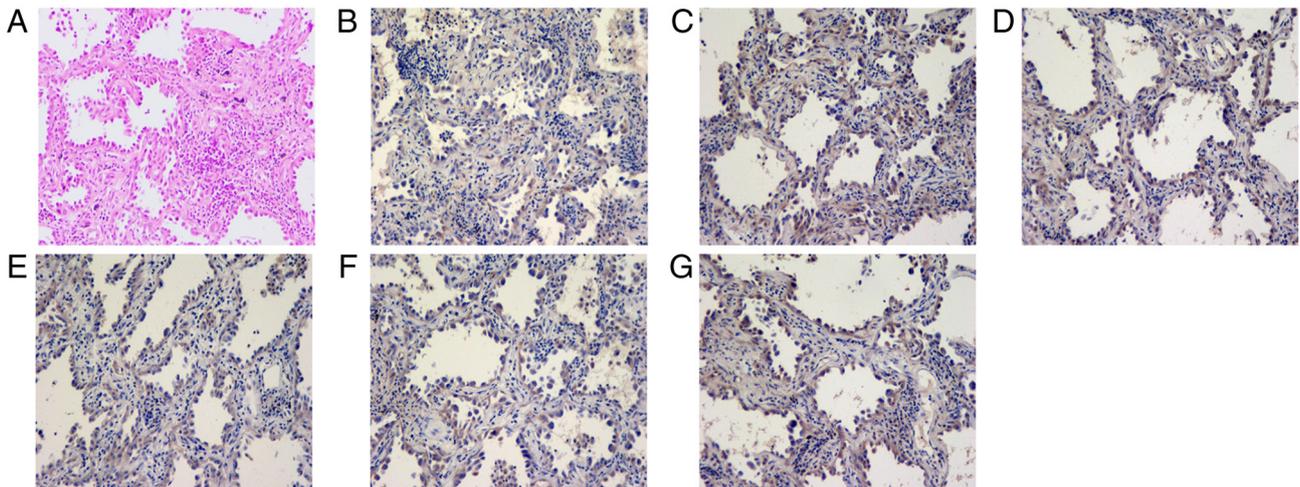


Figure 5. Immunostaining of lung tissue biopsy specimen for cytokines. (A) Hematoxylin and eosin. (B) CD38 positive. (C) CD39 positive. (D) CD73 positive. (E) CD138 positive. (F) CD203a positive. (G) TNF- $\alpha$  positive (magnification, x200 for all).

increase the sensitivity of anticancer drugs in RANK (+) MM cells (25). Kaiser *et al* (18) questioned whether CD38 blocking of lung tumor cells by dalamab would enhance the function of cytotoxic T cells.

The imbalance of the immune system is a focus of research in cancer studies. TNF- $\alpha$  serves an important role in the function, differentiation and transformation of B lymphocytes in MM, but it can also induce the apoptosis of myeloma cells (26). It is widely known that immune imbalance and proliferation are linked with carcinogenesis, and there is an association between the high expression of CD 38 and the degree of damage to immune system cells (27,28).

Among the published cases of MM complicated with lung cancer, the IgG type was dominant; one case was IgD type with poor prognosis, there was one case each of CD38 positive and CD138 positive and one case was strongly positive for CD38 and CD138, as shown in Table III. IgD multiple myeloma (IgD MM) is rare, accounting for ~1-2% of myeloma cases (29). Wang *et al* (19) reported a case of IgD MM complicated with lung cancer that was treated with surgery and anti-CD38 monoclonal antibody (daratumumab); the patient achieved complete remission. The case in the present study was also IgD MM and lung cancer was treated surgically, but the VDT scheme was

Table II. Analysis of the tumor markers.

Marker	Before treatment	After two cycles	After four cycles	Three months after ASCT	Reference values
CEA, ng/ml	1.14	0.930	1.150	1.510	<5.5
NSE, ng/ml	14.49	14.49	10.100	14.160	0-15
CYFRA21-1, ng/ml	2.11	2.50	3.640↑	2.950	<3.3
SCC, ng/ml	0.798	1.402	0.84	1.131	<2.5
AFP, ng/ml	None	None	None	5.250	<7
CA199, U/ml	None	None	None	10.380	<34
CA125, U/ml	None	None	None	36.180↑	<35
CA153, U/ml	None	None	None	16.670	<25
TPSA, ng/ml	None	None	None	1.590	<4.4

↑, Denotes above the upper limit of the reference range; None, not detected; CEA, carcinoembryonic antigen; NSE, neuron specific enolase; CYFRA21-1, cytokeratin 19 fragment; SCC, squamous cell carcinoma antigen; AFP,  $\alpha$  fetoprotein; CA199, carbohydrate antigen 199; CA125, carbohydrate antigen 125; CA153, carbohydrate antigen 153; TPSA, total prostate specific antigen; ASCT, autologous stem cell transplantation.

Table III. Analysis of multiple myeloma complicated with lung cancer.

First author (year)	Diagnosis	Immunohistochemical index	Treatment	(Refs.)
Ji (2004)	SCLC with MM (IgG- $\lambda$ stage I)	IgG (+), $\lambda$ light chain (+)	Radiotherapy, carboplatin, etoposide	(13)
Agarwal (2008)	MM ( $\lambda$ stage IIIA) with lung adenocarcinoma (stage IV)	CD38 (++) , CD138 (++) , CD56 (+) , $\lambda$ light chains (+) , CD19 (-) , $\kappa$ light chains (-)	Radiotherapy, carboplatins, taxanes	(11)
Marinopoulos (2008)	MM (IgG- $\kappa$ ) with NSCLC	A1/A3 (+) , TTF1 (+) , IgG- $\kappa$ (+)	Surgery, cisplatin, docetaxel, vinorelbine, topotecan	(20)
Goto (2010)	SCC (stage IB) with MM (IgG- $\lambda$ )	CD38 (+) , IgG (+) , $\lambda$ -light chain (+)	Surgery, dexamethasone	(16)
Lin (2010)	MM (IgA- $\lambda$ ) with SCC (stage IA)	IgA- $\lambda$ (+) , p53 (-) , VEGF ( $\pm$ ) , p16 (-) , CEA (-)	Cellular immunotherapy with CIK cells	(15)
Zuo (2017)	MM (IgG- $\kappa$ stage IIB) with lung adenocarcinoma (stage I)	CD138 (+) , IgG (+) , $\kappa$ light chain (+)	surgery, bortezomib, lenalidomide	(17)
Kaiser (2020)	MM with squamous subtype non-small cell lung cancer	None	Venetoclax, daratumumab, dexamethasone, pembrolizumab	(18)
Wang (2021)	MM (IgD) with lung cancer	IgD (+)	Daratumumab, surgery	(19)

+, positive;  $\pm$ , weekly positive; -, negative; SCLC, small cell lung carcinoma; MM, multiple myeloma; NSCLC, non-small cell lung carcinoma; SCC, squamous cell carcinoma.

adopted, autologous stem cell transplantation and long-term thalidomide treatment after operation. The patient has survived for >3 years.

In the patient, the immunohistochemical staining of CD38, CD138, CD39 and TNF- $\alpha$  were positive in both bone marrow and lung lesion. CD38 is one of the prognostic

factors in hematological cancers and a high level of CD38 has been detected in other cancers (30,31). Hogan *et al* (32) demonstrates a role for CD38 in immune modulation and confirms the multifaceted role of CD38 in the immune response in MM and lung cancer. Adenosine is important in immune regulation. CD38 regulates extracellular adenosine,

consumes NAD<sup>+</sup> and synthesizes adenosine through NAD<sup>+</sup>/CD203a/CD73, similar to ATP catabolism mediated by CD39/CD73 (32-34). Horenstein *et al* (35) also confirms this finding. Studies have shown that CD133<sup>+</sup> CXCR4<sup>+</sup> lung cancer stem cells evade immune monitoring by increasing the expression of CD38 and CD73 (36,37). Gao *et al* (38) confirm that lung cancer cells promote tumor progression by CD38-catalyzed cyclic ADP-ribose. These results indicate a role for CD38 in MM with lung cancer and provide an experimental basis for its use as a potential target. In addition, Bu *et al* (39) noted CD38 over-expression in lung cancer cells and tissues and that knockout of the CD38 gene reduced the occurrence of tumor in mice.

The present case expands our understanding of MM combined with NSCLC. CD38 may serve a role in MM and lung cancer by adenosine. Only one patient was reported in the present study and more studies of additional patients are required. In addition, further research is needed to explore the potential pathogenesis of the MM with lung cancer.

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### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

### Authors' contributions

YL is the principal responsible person of the study and substantially contributed to the conception and the design of the study. HHD and YL were accountable for all aspects of the work and contributed to the analysis and interpretation of the data, and also contributed to manuscript drafting critical revisions on the intellectual content. JL acquired and analyzed the data. LK and QW analyzed and interpreted the data. HHD, JL, LK, QW and YL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

All procedures were approved by the ethics committee of Hebei General Hospital (Shijiazhuang, China; approval no. 2022058). Written informed consent was obtained from the patient.

### Patient consent for publication

The publication of the article is with the informed consent of the patient.

### Competing interests

The authors declare that they have no competing interests.

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