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# Immunoglobulin D-Lambda Multiple Myeloma Initially Presenting in the Sphenoid Sinus, Orbital Apex, and Skull Base: A Systematic Review with a Case Report

Yihan Chen[1] Jianfeng Liu[1,2] Jianhui Zhao[2]

[1] China–Japan Friendship Hospital, Beijing University of Chinese Medicine, Beijing, People's Republic of China
[2] Department of Otolaryngology-Head and Neck Surgery, China–Japan Friendship Hospital, Beijing, People's Republic of China

**Address for correspondence** Jianfeng Liu, MD, PhD, Department of Otolaryngology-Head and Neck Surgery, China–Japan Friendship Hospital, 2 Yinghuadong Street, Chaoyang District, Beijing 100029, People's Republic of China (e-mail: mmconfucius@163.com).

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## Abstract

**Objectives** Multiple myeloma (MM) with initial manifestations in the sphenoid sinus, orbital apex, and skull base is exceedingly rare. A systematic review was conducted to investigate the epidemiology and advancements.

**Methods** Relevant cases were identified by searching CNKI, WanFang Data, CQVIP databases, PubMed, Embase, and Web of Science. Additionally, we present a case of IgD-λ (immunoglobulin D-lambda) MM with initial symptoms of dizziness, unilateral pain, blindness, and ophthalmoplegia, leading to a 4-month overall survival. Strictly based on PRISMA standards, we included and summarized existing cases and reflected our case.

**Results** Our systematic review includes 34 case reports, revealing 67.6% of patients initially presented with diplopia and 44.1% underwent endoscopic procedures, notably with only two cases of IgD-λ subtype. In our case, we performed an endoscopic wide trans-ethmoidal sphenoidotomy and biopsy of the skull base and orbital apex lesion. Postoperative pathology confirmed a highly active plasmacytoma, clinically diagnosed as IgD-λ MM with a TP53 deletion mutation and multiple extramedullary metastases. A range of diagnostic tools was employed, including hemoglobin, immunoglobulin, urinary protein analysis, positron emission tomography-computed tomography (CT), bone marrow cytology, and gene detection.

**Conclusion** The subtle clinical manifestations of IgD-λ MM in the paranasal sinuses and skull base hinder early diagnosis. There is a paucity of literature describing MM initially presenting in these locations. CT/magnetic resonance scans are necessary to identify characteristic bone destruction. An endoscopic approach is popular for tissue biopsy. Bone marrow biopsy with a smear, serum or urine protein electrophoresis, and immunofixation electrophoresis are crucial upon the appearance of target organ damage.

**Keywords**
- case report
- extramedullary metastasis
- multiple myeloma
- sphenoid sinus
- skull base

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## Introduction

Multiple myeloma (MM) is a hematological malignancy characterized by the uncontrolled proliferation of plasma cells within the bone marrow, leading to the production of monoclonal immunoglobulins (M proteins).[1] Immunoglobulin D-lambda (IgD-λ)-type MM exhibiting extramedullary involvement in the orbital apex, sphenoid sinus, and ethmoid sinus represents an exceptionally rare variant. The clinical symptoms and imaging manifestations associated with such cases are often nonspecific, which poses challenges that increase the likelihood of misdiagnosis or delayed diagnosis, and subsequently impact prognosis.[2] In recognition of the critical need for a more comprehensive understanding of this rare and diagnostically challenging subset of MM, we conducted a scoping review to enhance awareness, improve early diagnostic rates, and facilitate timely treatment. Additionally, we present a distinctive case of IgD-λ MM characterized by an initial presentation in the orbital apex, sphenoid sinus, and ethmoid sinus. This case serves to illustrate the complexities associated with this variant and emphasizes the importance of heightened clinical suspicion and accurate diagnostic approaches to achieve optimal patient outcomes.

## Materials and Methods

### Search Strategy

Our comprehensive research involved an exhaustive search across multiple databases, including CNKI, WanFang Data, CQVIP, PubMed, Embase, and Web of Science, extending up to August 31, 2023. The search strategy employed a combination of subject terms and free-text keywords, such as "multiple myeloma," "paranasal sinuses," "skull base," "plasma-cell myeloma," "Kahler disease," "nasal sinuses," "ethmoid sinus," and "sphenoid sinus." A detailed retrieval strategy can be accessed in ►**Supplementary Table S1** (available in online version only).

### Inclusion and Exclusion Criteria

Inclusion criteria: the following criteria were used to select articles for consideration:

- Case reports subsequent to January 1, 1980, and were available in Chinese or English.
- Cases in which MM initially manifested in the nasal sinuses and skull base, with a clear diagnosis based on the Multiple Myeloma Guidelines (2021) of the National Comprehensive Cancer Network (NCCN)[3] and the Guidelines for the Diagnosis and Management of Multiple Myeloma in China (2022 revision).[4] There were no gender or age restrictions.

Exclusion criteria: articles were excluded if they met any of the following criteria:

- Cases lacking an explicit diagnostic basis, those with a previous history of MM, or individuals who developed tumor lesions in other sites, experienced recurrence, or metastasis several months after the diagnosis of solitary extramedullary plasmacytoma, or with central nervous system involvement without lesions in the nasal sinuses or skull base were excluded.
- The absence of sufficient details in the description of at least four essential data points.
- Duplicate publications, studies lacking relevant data, or those inaccessible to researchers.

### Data Extraction

Data extraction encompassed the following elements:

- Basic study information: this category includes the study's title, Study ID, and other pertinent details.
- Case report details: this section systematically captured essential information on each case, encompassing details related to age, gender, chief complaints, lesion locations, surgical interventions, diagnosis criteria, MM subtype, treatment modalities, follow-up data, and prognosis.

## Results

### Systematic Scoping Review

A total of 526 records were initially retrieved and imported into NoteExpress 3.2.0. Following the removal of duplicate records, 492 unique articles remained. The researchers conducted an initial screening based on titles and abstracts, narrowing down the selection to 288 records. Subsequently, a thorough review of full-text articles led to the inclusion of 34 articles. The search process is presented in a visual summary in accordance with PRISMA guidelines (►**Fig. 1**). The final selection comprised 34 cases of MM patients who initially presented with lesions in the nasal sinuses and skull base. The male-to-female ratio was 19:15 among these cases. The majority of patients (67.6%) exhibited symptoms indicative of optic nerve, chiasma, or optic tract compression, such as diplopia, abnormal vision, or visual field disturbances at their initial presentation.

Surgical intervention was performed in 29 cases (85.3%), with 15 patients (44.1%) explicitly opting for endoscopic surgical approaches. The primary diagnostic methods employed included tissue biopsy, bone marrow examination, and serum/urine protein electrophoresis. The majority of patients underwent a combination of systemic chemotherapy and local radiotherapy, while a small number underwent autologous stem cell transplantation (ASCT).

Of the reported cases, 26 (76.5%) specified the MM subtype. It is noteworthy that only two cases (7.4%) involved IgD-λ-type MM, with one of these cases being female. Both IgD-λ patients succumbed within 12 months of diagnosis.

For a detailed account of the characteristics of the included cases, please refer to ►**Table 1**.

### Case Report

A 60-year-old female presented with a 1-month history of right-eye distending pain and diplopia, which had progressed to include blurred vision over the past week (May 2023). Furthermore, she also reported experiencing dizziness and an unexplained weight loss of exceeding 5 kg

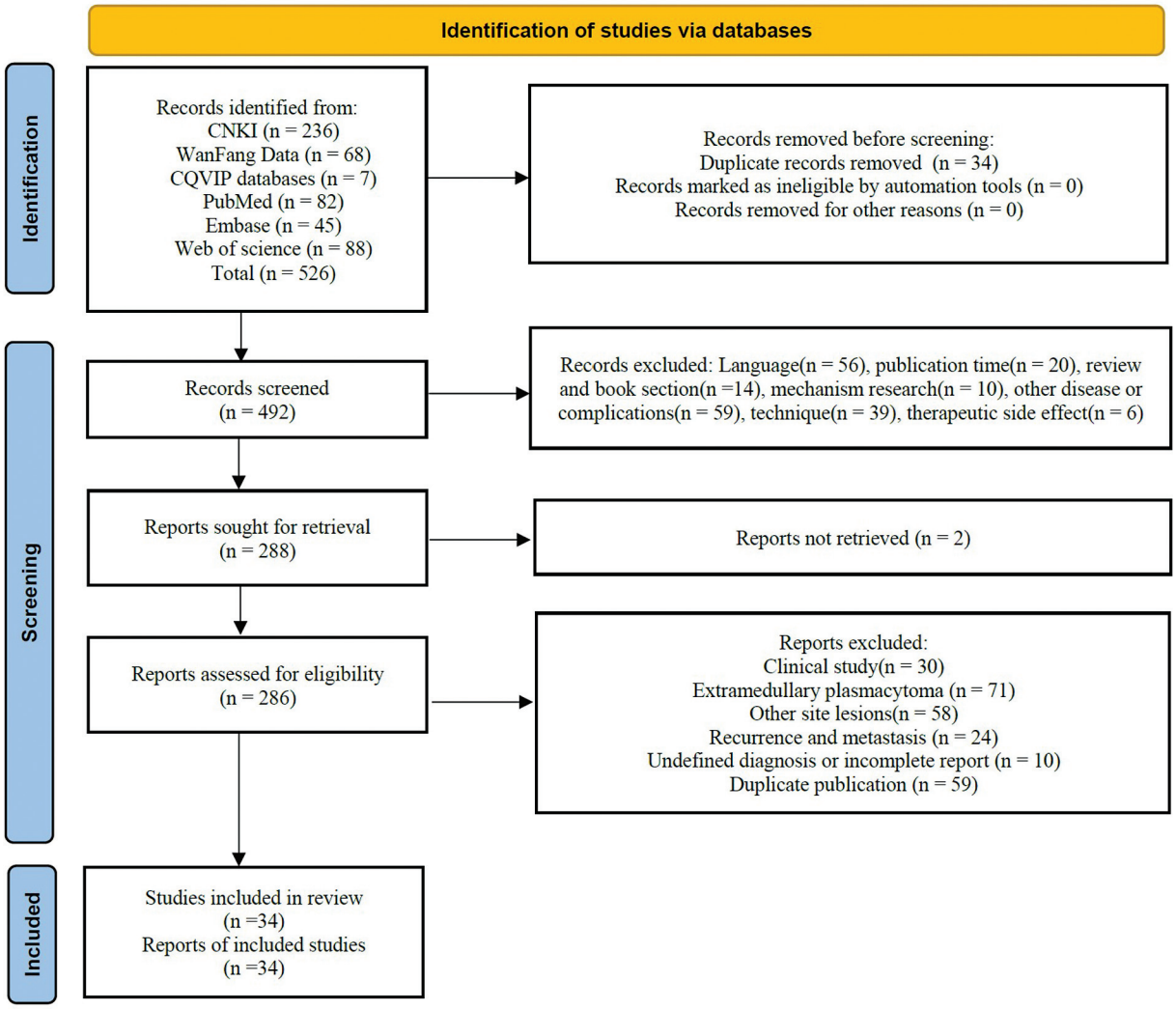


**Fig. 1** Search process depicted by the PRISMA flowchart.

over a period of 2 weeks. Notably, no symptoms were observed on the left side and no complaints of headache, nausea, or vomiting were reported. A visual assessment revealed a significant impairment, with acuity measurements of 0.02 in the right eye (OD) and 0.8 in the left eye (OS). The right eye exhibited ptosis, a fixed eyeball position, the absence of both direct and indirect light reflections, and visual field defects. Blood test results indicated a low red blood cell count ($3.32^{*}10^{12}$/L), hemoglobin (Hb; 98 g/L), and hematocrit (28.7%).

Radiological imaging (►**Fig. 2**): the computed tomography (CT) scan in axial, coronal, and sagittal views revealed the presence of a mass within the right posterior ethmoid and sphenoid sinuses, exhibiting no discernible evidence of bone destruction (A–C). The enhanced magnetic resonance (MR) in axial, coronal, and sagittal views shows the mass in the right posterior ethmoid and sphenoid sinuses. This mass displays a notable degree of enhancement and extends to the orbital apex and the skull base meninges and the cavernous segment of the internal carotid artery (D–F).

A space-occupying lesion was diagnosed in the right orbital apex, sphenoid sinus, and skull base based on the clinical findings. A subsequent biopsy was conducted via an endoscopic transnasal approach, which enabled access to the ethmoidal and sphenoid sinuses, and conducting a biopsy of the skull base and orbital apex. The frozen pathology indicated the presence of a malignant small round-blue cell tumor. Further exploration revealed the tumor had extended into the orbital apex, implicating the optic nerve eminence and the internal carotid artery eminence. The tumor was resected from the former two locations but not from the latter.

Histopathology and immunohistochemistry results indicated a highly active plasma cell tumor, with multiple myeloma oncogene-1 (MUM-1) (+)[B, 100 × ], CD138 (+) [C, 200 × ], a high proliferation rate as indicated by Ki-67% (MIB-1) (80% + )[D, 400 × ] and lambda light-chain restriction [E, 400 × ] (►**Fig. 3**). Minority of plasma cells demonstrate Kappa positivity [F, 400 × ], collectively signifying light-chain restriction. Sinus mucosa is infiltrated by sheets of extensive plasma cells [A, hematoxylin and eosin, 400 × ], displaying dislocated nuclei, high nu–plasma ratio, coarse nuclear chromatin, polymorphic nuclei, and occasional nucleolus. A positron emission tomography–CT scan identified

**Table 1** Basic characteristics of included cases

| Study ID (first author, year) | Age | Sex | Chief complaint | Lesion sites | Surgical intervention | Diagnostic basis | Subtype | Treatment | Follow-up (mo) | Prognosis |
|---|---|---|---|---|---|---|---|---|---|---|
| Liu 2013[48] | 26 | M | Bilateral ear stuffy, diplopia, headache, progressive numbness of both lower limbs | Mass in sphenoid sinus, abnormal signal in cervical medullary, and cavernous sinus | Endoscopic biopsy | 1, 3 | – | Chemotherapy (V) | 7 | Death |
| Shah, 2023[49] | 68 | M | Progressive blurred vision, periorbital pain, frontal headache, intermittent back pain | Centered in slope, extended to pituitary fossa, entered bilateral sphenoid sinus, and ethmoid sinus | – | 2, 4 | – | Chemotherapy (VCD) | 3 wk | Alleviate |
| Zuo, 2002[50] | 44 | M | Hoarseness, diplopia | Sphenoid and sella, bottom of sella, ethmoidal sinus | Biopsy | 1, 3 | – | Chemotherapy (M2), Intracranial radiotherapy | 7 | Improve |
| Wu, 2006[78] | 57 | M | Frontal headache, nausea | Posterior cranial fossa, straddling transverse sinus, skull base fracture | Open procedure excision | 1, 3 | IgG-λ | Chemotherapy | 3 | Stable |
| Qu, 2018[51] | 61 | M | Unilateral decreased vision | Left sphenoid sinus occupied with adjacent bone infiltration | Biopsy | 1, 3, 5, 6 | λ | Chemotherapy (BD-PACE), Allo-SCT intended | – | Improve |
| Chen, 2003 | 48 | M | Bilateral decreased vision, bone pain, dizziness, headache | Sella-slope occupation with skull base fracture | Endoscopic biopsy and excision | 1, 3, 4 | IgG-λ | Chemotherapy (VAD) | 1 | Improve |
| Lu, 2009[79] | 62 | F | Headache, unilateral double vision | Sellar region, occipital slope, with bone destruction | – | 3, 4, 5 | Light chain | Chemotherapy (TD) | 5d | Improve |
| Johnson, 2022[52] | 52 | M | Persistent visual changes, headache, epistaxis, fatigue | Invaded the cavernous sinus, displaced the internal carotid artery, extending to the middle cranial fossa, sphenoid sinus, posterior ethmoidal air chamber and slope, anterior pontine cisterna | Endoscopic biopsy and partial excision | 1, 3, 6, 7 | – | Local radiotherapy, Palliative radiotherapy, Chemotherapy (CyBorD, VRD), ASCT intended | – | VGPR |
| Silverman, 2022[53] | 60 | M | Intermittent diplopia, pain above the left eye, progressive ptosis | Left slope mass with cavernous sinus and slope extension with bone erosion | Endoscopic biopsy | 1, 2, 4 | IgG-λ | Pulse steroid + dexamethasone, local radiotherapy, Bortezomib intended | 5 | Death |
| Joshi, 2011[54] | 66 | M | Intermittent imbalance, right ear discomfort with hearing loss, dizziness, diplopia, right occipital headache, facial numbness | Mass located at the right apex of rock, destroyed the condyle of the right occipital bone, right side of the slope, body of the sphenoid bone, cavernous sinus, and apex of rock | – | 3, 4 | λ | Radiotherapy, cyclophosphamide, chemotherapy (VAD) | – | Alleviate |
| Ustuner, 2003[55] | 39 | M | Progressive paresthesia on the left side of the face and left arm, intermittent diplopia, dysphagia, hoarseness | Mass extends from the ethmoid and sphenoid sinuses to the junction of the slope and petroclival | Endoscopic biopsy | 1, 2 | Light chain | Local radiotherapy, chemotherapy (VAD), ASCT intended | – | Stable |
| Hogan, 2002[56] | 39 | M | Progressive loss of vision to amaurosis in the right eye, | Single epidural lesion of right orbital apex and sphenoid sinus | – | 2, 3 | IgA-λ | Chemotherapy (VAD), radiotherapy, Allo-BMT | 24 | Improve |

(*Continued*)

**Table 1** (*Continued*)

| Study ID (first author, year) | Age | Sex | Chief complaint | Lesion sites | Surgical intervention | Diagnostic basis | Subtype | Treatment | Follow-up (mo) | Prognosis |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | numbness in the left mandible, low fever, fatigue, frontal headache | near anterior bed process, optic nerve compression | | | | | | |
| Yamguchi, 2008[57] | 65 | F | Progressive diplopia | Mass invaded sinuses, slopes, rock apex and infratemporal fossa, slopes and sphenoid bone | Endoscopic biopsy and radical excision | 1, 3, 4 | IgA-λ | Local radiotherapy, chemotherapy (VAD), ASCT, thalidomide | 17 | Stable |
| Wein, 2002[58] | 60 | F | Left frontal headache, dacryorrhea with bulbar conjunctival edema | Invasive mass in the left supraorbital region involving the frontal and ethmoid sinuses | Biopsy | 1, 2 | – | Chemotherapy (VAD) | – | Alleviate |
| Wachter, 2010[19] | 43 | F | Acute unilateral vision loss | Mass in the left optic channel, wrapped optic nerve, calcification around the mass, sphenoid sinus, and cavernous sinus | Open procedure excision | 1 | λ | Local radiotherapy, intrathecal methotrexate, ASCT intended | 12 | Progress |
| Alegre, 1996[59] | 40 | F | Sudden diplopia and dysarthria | Enlarged basal bone tumor of the skull, destroyed the left petroclival region and extended to sphenoid sinus | Biopsy and partial excision | 1, 3 | – | Local radiotherapy, chemotherapy (VAD), PBSCT | 18 | CR |
| Kadiri, 2016[60] | 56 | F | Temporary headache, diplopia | Sphenoid sinus mass invades the sphenoid bone and extends to the left temporal region and cavernous sinus | Endoscopic biopsy | 1, 2, 4 | IgA-κ | Chemotherapy (dexamethasone + zoledronic acid), decompression radiotherapy | 8 | Death |
| Humphrey, 1983[61] | 60 | M | Left sixth nerve paralysis, left shoulder pain | Sphenoid sinus | Biopsy | 1, 4 | IgD-λ | Local radiotherapy, chemotherapy (M2) | 12 | Death |
| Hess, 2006[62] | 58 | M | Pain and swelling in the right jaw | Sphenoid sinus mass invaded nasopharynx | Biopsy | 1 | Light chain | Chemotherapy, radiotherapy, ASCT | – | Alleviate |
| Liu, 2023[63] | 54 | F | Dizziness, loss of right visual field with nausea and vomiting | Soft tissue mass in sphenoid sinus invaded occipital bone | – | 3, 5, 6 | IgD-λ | Chemotherapy (VCD, DVD-R, PLD, DEDP-R) | 9 | Death |
| Yazdanpanah, 2020[64] | 45 | M | Diplopia, headache, cough, and difficulty breathing | Involved sphenoid sinus and slopes, extending to the anterior pontine cistus and bilateral cavernous sinuses (left > right) | Endoscopic biopsy and excision | 2, 4, 6 | IgG-λ | Local radiotherapy, Chemotherapy (E-KRd) | – | Alleviate |
| Movsas, 2000[65] | 78 | F | Bilateral horizontal diplopia, headache, lameness in lower limbs | Slope mass, right cavernous sinus involvement, extending into sphenoid sinus, with bone destruction | Endoscopic biopsy | 1, 2, 4, 5 | IgG-κ | Local radiotherapy, chemotherapy (MP) | – | – |
| Bachmeyer, 1997[66] | 77 | M | Temporary loss of consciousness, intermittent horizontal diplopia | Invaded entire sphenoid sinus and destroyed sphenoid bone, extending to the ethmoid sinus, slope | Biopsy | 1, 2, 3 | IgG-λ | Radiotherapy, chemotherapy (MP) | 6 | Stable |

**Table 1** (*Continued*)

| Study ID (first author, year) | Age | Sex | Chief complaint | Lesion sites | Surgical intervention | Diagnostic basis | Subtype | Treatment | Follow-up (mo) | Prognosis |
|---|---|---|---|---|---|---|---|---|---|---|
| Oushy, 2018[67] | 59 | F | Ear distension, postural vertigo, pulsing tenderness in left ear, hoarseness, dysphagia | Internal lesion of left jugular foramen, tumor of left posterior occipital bone | Open procedure stereotactic biopsy | 1, 2, 4 | κ | Chemotherapy (VRd), ASCT | – | – |
| Reddy, 2021[68] | 52 | M | Unilateral diplopia, headache, sticky purulent discharge in the right ear, hearing impairment | Slope mass invaded the left cavernous sinus, multiple osteolytic lesions of the skull | Endoscopic biopsy | 1, 2, 4 | κ | Chemotherapy (VCD), local palliative radiotherapy | – | Alleviate |
| Patel, 2010[69] | 42 | F | Occipital headache, nausea, vomiting | Posterior fossa mass, osteolytic destruction of occipital bone, compression of Sylvius aqueduct and fourth ventricle, with hydrocephalus | Open procedure | 1, 2, 4 | IgG-λ | Steroid, cytotoxicity, radiotherapy | – | – |
| Rahman, 2016[70] | 84 | F | Headache, blurred vision, progressive bilateral horizontal diplopia | Slope mass extends to the sphenoid and posterior ethmoid sinuses | Endoscopic biopsy | 1, 2 | λ | Radiotherapy, chemotherapy (V) | – | – |
| How, 2019[71] | 29 | F | Distension, hearing loss, unilateral pulsating tinnitus, loss of taste | Central mass of the right jugular foramen with extensive bone destruction and an erosive appearance | Open procedure biopsy and excision | 1, 2, 4, 6, 7 | IgA-κ | Dexamethasone + local palliative radiotherapy, chemotherapy (KRd) | – | Alleviate |
| Magrassi, 2016[72] | 57 | M | Sudden diplopia, dizziness | Osteolytic clival disease extending to both the great wings of the sphenoid bone and the right petrous bone, with partial involvement of the inner ear | Stereotactic biopsy | 1, 2 | IgG-κ | Radiotherapy, chemotherapy | – | – |
| Du, 2015[77] | 47 | F | Frontal headache, eye distention | Mass in the sphenoid sinus, partial fracture of the sinus wall | Endoscopic biopsy | 1, 3, 4 | IgG | Chemotherapy | – | Alleviate |
| Shenoy, 2010[73] | 58 | M | Left side hearing loss, dizziness, headache | Slope mass invaded rock apex, left jugular bulb, and left cerebellar cornual cisterna extending to left sigmoid sinus | Endoscopic biopsy | 1, 3, 4 | – | Chemotherapy (TD), local radiotherapy, BMT | – | – |
| Rezazadeh, 2005[74] | 62 | M | Progressive cervical pain and diplopia | Slope mass extends to the brain stem, left inner ear and internal carotid artery canals, nasopharynx, sphenoid bone, cavernous sinus | Endoscopic stereotactic biopsy | 1, 3, 4, 5 | κ | Dexamethasone, radiotherapy | – | – |
| Higurashi, 2004[75] | 53 | F | Diplopia, left abducent paralysis | Osteolytic mass in the left petroclival region invaded left internal carotid artery | Open procedure radical excision | 3 | – | Chemotherapy, ASCT | 30 | Stable |
| Nofsinger, 1997[76] | 79 | F | Unilateral blurred vision and diplopia | Slope mass extends to right sphenoid sinus | Endoscopic biopsy | 1, 2 | IgG-κ | Chemotherapy, local radiotherapy | – | Alleviate |

(*Continued*)

**Table 1** (*Continued*)

| Study ID (first author, year) | Age | Sex | Chief complaint | Lesion sites | Surgical intervention | Diagnostic basis | Subtype | Treatment | Follow-up (mo) | Prognosis |
|---|---|---|---|---|---|---|---|---|---|---|
| Chen, 2023[80] | 60 | F | Distending pain and diplopia of unilateral eye, blurred vision | Lesions in ethmoid sinus and sphenoid sinus, orbital apex with bone absorption | Endoscopic biopsy and partial excision | 1–7 | IgD-λ | Chemotherapy (VRd*1, D-PAD*2) | 4 | Death |

Abbreviations: Allo-BMT, allogeneic bone marrow transplantation; Allo-SCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplantation; BCD/VCD/CyBorD, Cyclophosphamide, Bortezomib, and Dexamethasone; BD-PACE, Bortezomib, Dexamethasone-Cisplatin, Cyclophosphamide, Etoposide, and Adriamycin; BMT, bone marrow transplantation; CR, complete response; DEDP-R, Dexamethasone and Lenalidomide; D-PAD, Daratumumab-Bortezomib, Doxorubicin liposomes, and Dexamethasone; DVD-R, Bortezomib, Lenalidomide, Pegylated liposomal doxorubicin, and Dexamethasone; E-KRd, Elotuzumab-Carfilzomib, Lenalidomide, and Dexamethasone; F, female; KRd, Carfilzomib, Lenalidomide, and Dexamethasone; M, male; M2, Carmustine, Cyclophosphamide, Vincristine, Melphalan, and Prednisone; MP, Melphalan and Prednisone; PBSCT, peripheral blood stem cell transplantation; PLD, Bortezomib, Lenalidomide, Pegylated liposomal doxorubicin; TD, Dexamethasone and Thalidomide; V, Bortezomib; VAD, Vincristine, Adriamycin, and Dexamethasone; VGPR, very good partial remission; VRD/VRd, Bortezomib, Lenalidomide, and Dexamethasone.

Note: 1: tissue biopsy; 2: bone marrow biopsy; 3: bone marrow aspiration/smear; 4: serum/urine protein electrophoresis; 5: immunofixation electrophoresis; 6: FISH; 7-PET-CT. "Alleviate" means symptoms have improved, but the lesions were not reduced or eliminated.




**Fig. 2** **Radiological imaging.** CT shows a mass in the right posterior ethmoid and sphenoid sinuses, with no obvious bone destruction (**A–C**). Enhanced MR shows the mass enhances significantly and extends to the orbital apex and the skull base meninges and the cavernous segment of the internal carotid artery (**D–F**). CT, computed tomography; MR, magnetic resonance.

a hypermetabolic mass in the vicinity of the iliopsoas muscle within the right pelvic cavity, in addition to multiple bone lesions with increased metabolism, anemia, and splenomegaly. Bone marrow aspiration and biopsy confirmed a segment of the pulp cavity devoid of activity, along with a widespread proliferation of plasma cells, consistent with plasma cell myeloma. Fluorescence in situ hybridization (FISH) revealed a TP53 deletion in 96% of cells at the 17p13.1(0) and 11q22.3 (G) sites.

Subsequent to the biopsy and confirmation of the pathological diagnosis, the patient was referred to the hematology department for further treatment. The clinical diagnosis was IgD-λ MM, classified as either IIIa stage (DS stage) or II stage (R-ISS stage), with a TP53 deletion mutation and multiple extramedullary metastases, including a skull base mass and a right iliopsoas muscle mass.

After a course of VRd chemotherapy (Bortezomib, Lenalidomide, and Dexamethasone), the patient's right-eye vision improved somewhat, accompanied by a reduction in right waist and leg pain. A D-PAD (Daratumumab-Bortezomib, Doxorubicin liposomes, and Dexamethasone) regimen was subsequently administered. However, following three cycles of both VRd and D-PAD, the patient developed progressive weakness in the bilateral lower extremities, loss of acupuncture sensation, and muscle strength deficits in both proximal and distal areas. Tendon reflexes in the bilateral lower extremities were absent, and deep sensation below the hip

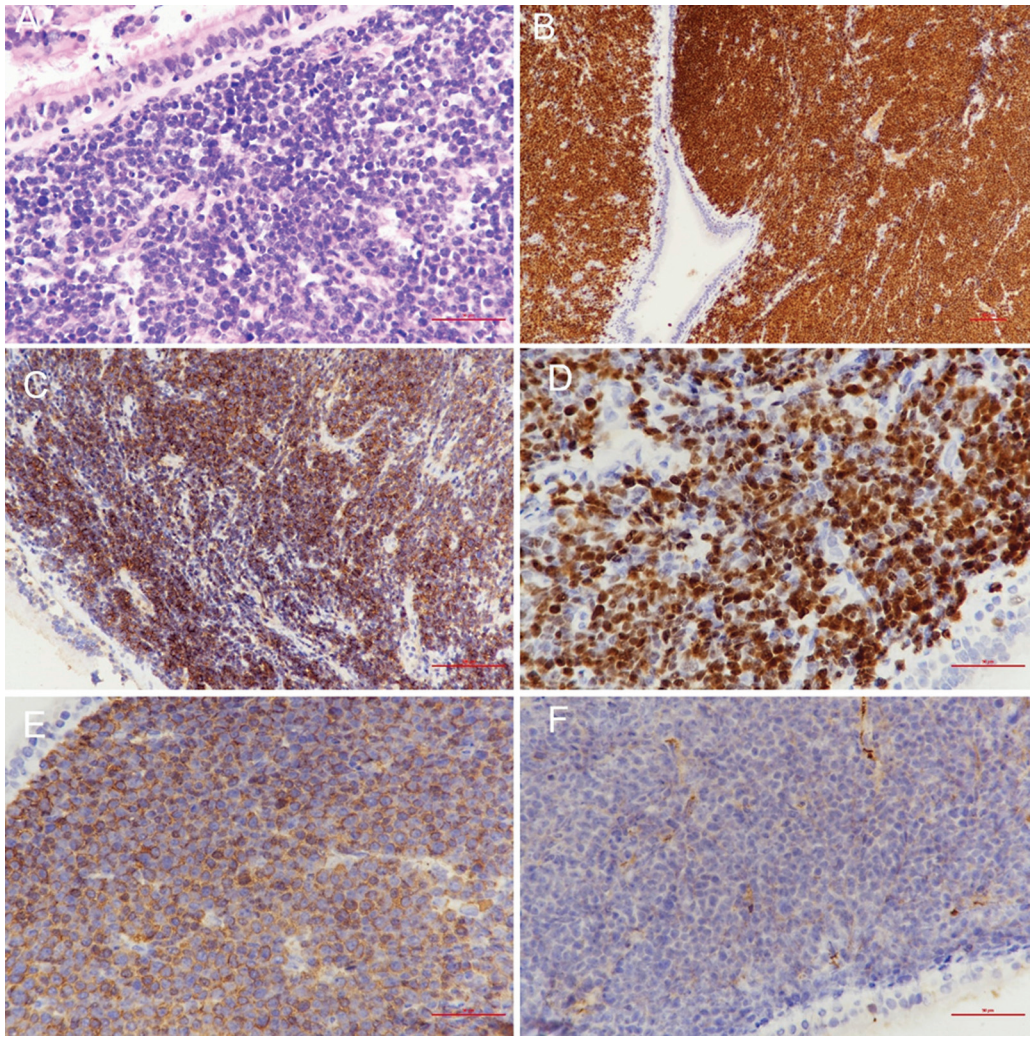


**Fig. 3** Histopathology and immunohistochemical profile of the sphenoid sinus mass.
Highly active plasma cell tumor [**A**, hematoxylin and eosin (H&E), 400 × ].
MUM-1(+) [**B**, 100 × ], CD138(+) [**C**, 200 × ] and Ki-67% (MIB-1) 80%+ [**D**, 400 × ].
Light-chain restriction of Lambda [**E**, 400 × ] and Kappa [**F**, 400 × ].

joint was lost. A MR imaging (MRI) of the cervical, thoracolumbar region revealed the presence of lesions in the vertebrae, which were diagnosed as intraspinal extramedullary plasmacytoma exerting pressure on the thoracic spinal cord. Surgery was proposed but declined by the family. Maintenance chemotherapy with Doxorubicin liposome and Dexamethasone was administered, but the patient's condition did not significantly improve. Due to financial limitations, Selinexor was not pursued, and symptomatic supportive treatment was offered.

At this juncture, the patient's ocular symptoms had subsided, and vision had largely been restored. However, chemotherapy proved less effective, and new extramedullary lesions emerged in the context of highly malignant circumstances. A clear and effective therapeutic regimen was not available, and the patient's life expectancy was estimated at 3 months. The patient chose to return to her local area to alleviate suffering and passed away in September 2023.

## Discussion

### Epidemiology

MM stands as the second most prevalent hematological tumor globally, with a higher incidence in males than in females and a mean age of onset of 57 years. Although the occurrence of IgD and nonsecreted types of M protein is infrequent, research conducted in Europe and the United States has demonstrated that IgD accounts for a mere 1 to 2% of all MM cases.[1,5] In contrast, this proportion is slightly higher in China, accounting for 5.2,[6] 6.9,[7] and even 11.7%.[8] IgD MM can be further categorized as λ (60–95%[9–11]) and κ based on the light chain type. Extramedullary disease (EM) is typically observed as a solitary case, and MM complicated with EM is uncommon. Among the 40 patients with MM and EM observed by Chen et al,[12] IgD MM accounted for only 10%. Extramedullary invasion occurred in 4% of the 664 MM cases reported by García-Sanz et al.[13] The patient we reported, a 60-year-old female with sphenoid sinus, orbital apex, and

skull base as the initial sites, represents a relatively rare clinical presentation that is prone to misdiagnosis and missed diagnosis.

## Clinical Manifestation

MM typically presents with a constellation of symptoms collectively known as "CRAB", which encompass hypercalcemia, renal insufficiency, anemia, and bone destruction. Alternatively, it may manifest as an extramedullary plasma cell tumor, Bence–Jones protein in urine, weight loss, and other symptoms.[14] This wide range of symptoms can pose diagnostic challenges, given the diverse range of specialties involved. Bone pain is the initial presenting symptom in over 80% of MM patients.[15] Additionally, there have been reports of unconventional presentations, including central retinal vein obstruction,[16] hoarseness,[17] anaphylactoid purpura,[18] and vision loss.[19] In comparison to other types of MM, IgD MM is more likely to develop extramedullary infiltration.[20] The incidence of IgD-λ MM patients with EM at the initial diagnosis is approximately 7 to 18%, and the occurrence of EM during treatment is approximately 6 to 20%.[21–23] The patient we presented displayed evident ocular symptoms during the initial consultation, with imaging diagnostics revealing a mass occupying both the ethmoid and sphenoid sinuses, accompanied by osteolytic lesions located at the orbital apex. Further investigation is necessary to reach an accurate diagnosis.

## Laboratory Examination

When Hb decreases, and globulin increases, but no significant abnormalities in white blood cell count or classification are evident in routine tests, serum immunoglobulin detection, serum protein electrophoresis (SPE), and blood/urine light chain detection should be performed in a timely manner.[24] In instances where there is a reduction in lipid levels,[25] decline in peripheral blood lymphocyte count, and an elevation in uric acid levels,[26] it is imperative that clinicians exercise heightened vigilance and undertake a comprehensive bone marrow analysis.

The identification of the M protein in either blood or urine is a crucial element in the diagnosis of MM. It is important to note that the absence of an M protein peak in SPE does not rule out MM. Immunofixation electrophoresis is a more effective diagnostic tool than SPE and urine Bence–Jones protein,[27] serving as the industry standard for identifying and classifying protein types through immunochemical techniques.[28] Additionally, serum-free light chain immunoassay is an early indicator for assessing efficacy and detecting minimal residual disease (MRD).[29] Another recently introduced index is β2-microglobulin, which is employed to assist in the diagnosis and evaluation of MM treatment effectiveness.

However, 5 to 10% of patients do not excrete M protein, which can result in clinical diagnosis difficulties.[30] Bone marrow analysis remains an indispensable test for the final determination of MM. Increased quantities of myeloma cells (MCs) can be observed in bone marrow aspiration and smear. Bone marrow biopsy can help eliminate misdiagnosis caused by localized hyperplasia lesions. Thus, bone marrow biopsy combined with smear is an effective means to improve the detection rate of MM.[31] Chromosomal translocations and IGH gene mutations detected by FISH are related to MC morphology, clinical subtypes, disease progression, chemotherapy sensitivity, and prognosis.[32] For instance, the deletion of 17p13 leads to the loss of tumor suppressor gene p53, resulting in poor prognosis, severe conditions, plasma cell tumors, and hypercalcemia.[33]

## Histopathology

Histopathology is widely considered the definitive method for the diagnosis of MM. In cases where masses in the head and neck are difficult to diagnose, a pathological biopsy can be a quick and effective diagnostic tool. It does the need for a reminder that SRBCT (small round blue cell tumor) requires taking a conservative and thorough approach before rendering a diagnosis because of the pathological characteristics.[34,35] CD138 is a surface antigen specific to MC and is utilized as an early detection marker in 100% of cases.[36,37] Although CD38 also highly expresses in MC and myeloma stem cells, normal plasma cells express both markers as well.[38] CD56 is expressed in abnormal plasma cells, while CD19 is expressed in normal plasma cells but not or at low levels in MM cells. Malignant plasma cells are more likely to express CD56(+)/CD19(−), which enhances the combined specificity.[39] CD138, CD79α, and Cyclin D1 are highly expressed in MM. CD138, CD79α, and Cyclin D1 can be used as powerful diagnostic tools when no characteristic tumor cell space-occupying lesions are found in bone marrow samples.[40]

## Imaging Manifestation

Regarding the intracranial involvement of MM extramedullary metastasis, CT can visually observe the bone destruction around the masses, and MRI can enable early detection of the soft tissue masses and assess the extent of mass infiltration. CT manifestations in MM with sphenoid sinus lesions typically include irregular soft tissue masses in the sphenoid sinus region presenting as isodensity, with poorly defined boundaries and peripheral osteolytic bone destruction.[41] The surrounding bone of lymphoma of sinus origin is predominantly characterized by insect erosion and osteolytic destruction, with a greater scope of soft tissue invasion than bone destruction.[42] The bone destruction is less severe than that observed in other sinus malignancies.[43] While the MR signal strength is nonspecific, the apparent diffusion coefficient can be used to initially identify the area.[44,45]

## Diagnosis

Diagnosing active MM follows established criteria outlined in the Multiple Myeloma Guidelines (2021) of NCCN and the International Myeloma Working Group guidelines. The aforementioned diagnostic criteria encompass the following elements: (1) a bone marrow biopsy revealing a proportion of plasma cells $\geq$10% or confirmation of plasmacytoma through biopsy of other tissues. (2) The presence of M protein in either serum or urine. (3) Identification of the "CRAB"

symptoms, which includes C for hypercalcemia (serum calcium > 2.75 mmol/L), R for renal insufficiency (serum creatinine > 177 μmol/L), A for anemia (Hb < 100 g/L), and B for bone destruction, as indicated by the presence of single or multiple osteolytic lesions upon imaging examination. A diagnosis of active MM is made when criteria (1) and (2) are present, and at least one of the criteria outlined in (3) is met.[46,47] Clinical staging systems, including Durie–Salmon, the International Staging System (ISS), and the Revised ISS (R-ISS), are frequently employed for the assessment of the disease extent. In the case we presented, the diagnosis was rigorously established following a comprehensive analysis.

### Treatment

Effectively managing active MM necessitates a multifaceted approach that encompasses initial treatment, the prevention of bone disease, and symptomatic supportive care. For patients in good physical condition, ASCT is the preferred course of action following effective induction therapy. Induction therapy typically involves a three-drug combination regimen incorporating protease inhibitors (PIs) such as Bortezomib, immunomodulators (iMiDs) like Lenalidomide, and Dexamethasone. This regimen is primarily employed to initiate treatment. In some cases, a four-drug regimen, including the addition of Daratumumab, can yield improved postinduction outcomes, particularly with regard to MRD conversion. In instances of recurrent or refractory MM, a range of treatment options is considered, including PIs, iMiDs, Daratumumab, exportin 1 inhibitors (XPO1), such as Selinexor, and cytotoxic agents like Doxorubicin liposomes, with the overarching goal of enhancing patients' overall quality of life.[4]

## Conclusion

Early diagnosis is crucial in IgD-λ MM presenting in the sphenoid sinus, orbital apex, and skull base due to its rapid progression and generally poor prognosis. Symptoms like diplopia and anemia should raise suspicion, prompting imaging for diagnosis. CT/MR scans show high-grade malignancy with characteristic bone destruction, necessitating a biopsy for definitive diagnosis. The trans-nasal endoscopic approach is favored due to minimal surgical trauma, requiring familiarity with localized anatomy. Recognition of anemia, lipid-level changes, and organ damage warrants thorough examination, including immunoglobulin assessment and bone marrow biopsy. For progressive cases, early induction chemotherapy followed by marrow transplantation post-surgery is recommended. Regular follow-up and symptomatic support are essential components of patient care.

### Trial Registration

Chen, Y., Liu, J. (September 12, 2023). Immunoglobulin D-Lambda Multiple Myeloma Initially Positioning in Orbital Apex and Skull Base: a Case Report and Scoping Reviews. Retrieved from: https://osf.io/wzafy// DOI: 10.17605/OSF.IO/WZAFY.

### Author Contributions

J.L. was responsible for conceptualization, funding acquisition, project administration, supervision, and writing (review and editing). Y.C. handled data curation, formal analysis, investigation, methodology, resources, software, validation, visualization, and writing (original draft) and J.H. contributed to investigation, resources, and visualization.

### Ethical Statements

The case study has gained institutional approval and informed consents.

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### Conflicts of Interest

None declared.

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