Immunoglobulin D Multiple Myeloma in Our Hospital - A Rare Occurrence

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ABSTRACT

Immunoglobulin (Ig) D multiple myeloma is a rare presentation, usually with an aggressive course and a poorer prognosis. It accounts for about 1-2% of newly diagnosed mulitple myeloma patients. Due to its rarity, reports on Ig D multiple myeloma are limited in the literature. We therefore present 4 cases of Ig D multiple myeloma in our hospital over a period of 8 years between 1990 to 1998. The average age of presentation of our patients was 44 years old with a female preponderance. Common presenting symptoms were appetite and weight loss and bone pain. Two patients presented with neurological symptoms and 2 with renal impairment. Three patients had an associated lambda paraproteinaemia and the fourth had a kappa paraproteinaemia. A common finding in Ig D myeloma is a small or no spike seen on serum electrophoresis together with heavy Bence Jones proteinuria. A review of the literature on Ig D myeloma is also presented.

Keywords : Ig D, multiple myeloma

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INTRODUCTION

Immunoglobulin D was first described by Rowe and Fahey[1] in 1960s. The role of Ig D as an immunoglobulin is still not well understood. It is first immunoglobulin detected on the surface of developing B lymphocytes. The number of Ig D multiple myeloma are few, accounting for less than 2% of new cases. There are only 3 large reviews in the literature of Ig D multiple myeloma cases since the discovery of immunoglobulin D. Due to its uncommon occurrence, an understanding of this subtype will become increasingly more evident as more cases continue to be reported. We report 4 such cases in our hospital over the last 8 years and review its manifestations in relation to what has already been reported of this subtype of multiple myeloma.

CASE HISTORIES

Case 1

A 44-year-old Chinese woman (WPH) presented in June 1990 with a 3 months' history of low back pain, generalised weakness, appetite loss and weight loss. She also described a short history of bilateral lower costal pain and was found to have a 3cm hepatomegaly. A lumbar spine CT Scan revealed a lateral disc prolapse at L5/S1 with the disc material encroaching into the neuroforamina. Skeletal survey showed multiple lytic lesions involving the long bones and pelvic bones. Blood, serum, urine and bone marrow investigations (see Table I) confirmed the diagnosis of Ig D myeloma. She was started on oral chemotherapy (melphalan and prednisolone) and interferon was later added to her treatment. Unfortunately, no further information of her illness could be obtained as she defaulted after her second clinic visit.

Table 1. Investigations of our 4 cases of Ig D Myeloma.

Investigations	Case 1	Case 2	Case 3	Case
Age (yrs)	44	73	31	39
Sex (M/F)	F	F	F	M
Hb (g/dl)	7.2	11.3	8.9	8.4
ESR (mm/hr)	140	11	150	120
Bone marrow Plasma cells (%)	94	6	50	84
Calcium (mmol/l) (2.15-2.55)	2.28	2.63	2.06	3.11
Urea (mmol/l) (2.0-6.5)	4.2	11.3	4.7	14.9
Creatinine (umol/l) (65-125)	–	165	93	778
Total protein (g/l) (65-82)	76	54	67	64
β2-microglobulin (ug/1) (<1900)	–	10177	3973	3529(
Urate (mmol/l) (220-450)	611	–	607	704
Cr Clearance (ml/min) (75-135)	–	18.49	–	21.47
Urine Protein (g/day) (<0.2)	–	5.42	–	7.27
Serum and Urine Electrophoresis	2 bands Ig D λ and free λ	2 bands Ig D κ and free κ	2 bands Ig D λ and free λ	2 banc Ig D λ and f

Case 2

A 73-year-old Chinese lady (GKS) was admitted in November 1993 from a nursing home with almost a year's history of persistent back pain, appetite and weight loss, and personality change noticed by the nursing home. Clinically, she had tenderness and angulation at L1 level with reduced sensation from the mid-spine downwards. She also had absent lower limb reflexes with down-going plantars. No loss of power was detected in both her lower limbs. Lumbar spine X-ray showed compression fracture at L1 vertebra and MRI scan revealed enhancement of T12, L1 and L2 with a paravertebral soft tissue mass. There was partial collapse of L1 and cord compression. CT guided biopsy of the paravertebral mass was non-diagnostic. Other investigations which included a bone marrow examination, blood, serum and urine protein electrophoresis (see Table I) confirmed Ig D myeloma. As she was in acute urinary retention due to cord compression, she was treated with spinal radiotherapy and dexamethasone. She was also started on oral chemotherapy (melphalan and prednisolone). There was only minimal response after 3 courses of chemotherapy and her family opted for palliative care. Shortly after, she passed away peacefully.

Case 3

A 31-year-old Fillipino house maid (AGO) was admitted in March 1997 with a week's history of non-traumatic back pain associated with lower limb weakness, difficulty in walking, altered sensation, and difficulty passing urine. She also noticed weight loss and appetite loss. Clinically, she was in acute urinary retention with a palpable bladder. Her perianal sensation was normal but she had a laxed anal tone. No spinal tenderness could be elicited. She was found to have reduced sensation from L1 level downwards and reduced power in both lower limbs. Lower limb reflexes were brisk with downgoing plantars. She was thought to have Cauda Equina syndrome with acute urinary retention. A thoracic MRI scan revealed a right posterolateral intradural extramedullary mass extending from T6 to T9 level with a 10 mm x 14 mm tight paravertebral component at T7. Emergency surgical decompression of her spinal cord was performed with excision of the extramedullary mass. Histology confirmed myelomatous involvement. Blood, bone marrow examination, serum and urine protein electrophoresis (see Table I) confirmed Ig D myeloma. Post-operatively, she returned to the Philippines for further medical treatment. She was advised to have radiotherapy to her thoracic spine for residual disease as well as combination chemotherapy such as vincristine, adriamycin and dexamethasone (VAD).

Case 4

A 39-year-old Chinese man (OKS) was referred in March 1998 to the renal outpatient clinic with a 4 months' history of myalgia, rib and back pain as well as appetite loss and weight loss. Clinical examination revealed a low grade pyrexia without a clinical source of infection. Neurological signs were not elicited and there was no organomegaly. Investigations included blood, bone marrow examination, serum and urine electrophoresis (see Table I) confirmed that he had Ig D myeloma. Skeletal survey revealed extensive lytic lesions in all his bones and ultrasound scan of his abdomen revealed a mild splenomegaly. He was treated initially with 5 days of intravenous high dose methylprednisolone and 3 days of total plasma exchange as a salvage procedure for his renal impairment. Following this, there was a marked improvement in his renal function. He was also started concurrently on combination chemotherapy, C-VAMP (cyclophosphamide, vincristine, adriamycin and methylprednisolone). Following 3 courses of treatment, a reassessment of his disease status showed complete remission with improvement of his disease markers and creatinine clearance as well as resolution of his proteinuria (see Table II). Allogeneic bone marrow transplantation was considered but due to his suboptimal renal function and social difficulties, this was not a suitable option for him. In August 1998, 5 months after his diagnosis, he was given high dose chemotherapy with melphalan and methylprednisolone and received an autologous peripheral stem cell transplantation. Apart from a Klebsiella pneumoniae septicaemia, he had an uncomplicated post-transplant course and had bone marrow engraftment by 2 weeks. We hope to proceed to a second transplantation within the next 6 months.

Table II. Serial Investigations of Case 4 (OKS).

Investigations	Diagnosis	1 week	3 months	5 months
Urea (mmol/l)	14.9	12.7	6.5	–
Creatinine (umol/l)	778	279	148	–
Cr Clearance (ml/min)	21.47	–	39.30	44.00
Urinary Protein (g/day)	7.27	–	0.27	<0.20
β2-Microglobulin (ug/l)	35290	10100	3229	–
Ig D (g/l) (0.80-2.00)	23.000	–	0.017	0.024
Bone Marrow Plasma Cells (%)	84	–	2	–

DISCUSSION

Immunoglobulin (Ig) D was first described by Rowe and Fahey in 1965[1]. It usually presents as an absent spike or a small spike in the gamma or beta zone on serum electrophoresis and an associated heavy Bence Jones proteinuria. When a myeloma panel is requested in our laboratory, high resolution electrophoresis is performed

on both urine and serum samples and the proteins are quantitated using nephelometry. If only a light chain band is detected, further analysis is carried out to detect the rarer presence of Ig D or Ig E paraproteins. Ig D plasma cell dyscrasias are uncommon over the last 8 years (1990 to 1998), there are only 4 cases of Ig D multiple myeloma in our hospital. The most common subtype is Ig G myeloma. This is followed by Ig A myeloma and light chain disease. Ig D myeloma accounts for only 1-2% of newly diagnosed multiple myeloma cases. Only 3 large reviews of Ig D myeloma are reported in the literature. The first report was from Toronto on 133 cases of Ig D myeloma in 1975[2]. The next report was almost 20 years later where the Japanese looked at 165 patients in 1991 and established a new risk grouping for Ig D myeloma[3]. The most recent review in 1994 was from a single institution, Mayo Clinic, on 53 patients looking at its clinical presentation, treatment response and survival[4]. Due to its rarity, case reports on Ig D myeloma are invaluable in our future understanding of this subtype of multiple myeloma.

Multiple myeloma patients tend to present in their mid-60s but the age of presentation of the subtype Ig D myeloma is much younger and similar to those with light chain disease[2]. These patients are usually 4 to 9 years younger than those with Ig G or Ig A subtypes[5,6]. The average age of our 4 patients was found to be 44 years. 3 of our patients were females but previous reviews have shown a male preponderance[2,3,4]. Similar to other subtypes of myeloma, the most common presenting symptoms are bone pain, constitutional symptoms and neurological manifestations[2,3,4]. These symptoms were common among our patients and 2 of them presented with symptoms of sensory loss of their lower limbs, cord compression and urinary retention. Extraosseous involvement is a common presentation in Ig D myeloma and is reported in 27% to 63% of cases[3,5]. Amyloidosis is also commonly seen, as high as 44% in one series[2]. Half of the patients with Ig D myeloma are known to have organomegaly and lymphadenopathy[2]. One of our patient had a clinically detected hepatomegaly (WPH) and the other (OKS) was found to have splenomegaly on ultrasound scanning. Osteolytic lesions are commoner in Ig D myeloma and reported in 75% of patients[2]. Extensive bone involvement was seen in 2 of our patients. Hypercalcaemia is commonly found in Ig D myeloma and noted in a third of cases[7]. Immuneparesis is also present in the majority of patients[8]. Two of our patients presented with hypercalcaemia and all of them were found to have immuneparesis. In the Japanese review[3], haemoglobin, serum creatinine, paraprotein level, bone marrow plasma cell percentage and platelet count did not play a significant predictor of severity of disease[3]. They were able to stratify their patients into 3 risk groups based on light chain subtype and presenting white cell count[3]. They found that kappa subtype and a total white cell count of less than 7 x 10^9/l to be of a low risk group and lambda expression with a total white cell count of more than 7 x 10^9/l to be of a high risk group.

Associated light chain disease is commonly seen among Ig D myeloma patients[3] but found in only 16% to 33% of patients with Ig G or Ig A myeloma[5]. About 80 - 94% of Ig D myeloma patients have lambda light chain subtype[4] as compared with only one third of the cases in Ig G or Ig A myeloma. Similar findings were found in our cases, with 3 patients having lambda light chain expression. The characteristics of kappa and lambda light chain disease do not show any significant difference[4]. In one series[2], Bence Jones proteinuria is detected in 92% of patients. This was noted in all our patients. It is felt that Ig D myeloma may be considered as a variant of light chain disease as they both have similar characteristics[4]. Renal impairment is reported in 67% of Ig D myeloma patients[8]. 2 of our patients were found to have renal insufficiency. In the Nordic myeloma group of 1353 patients, all patients with Ig D myeloma and half of the light chain disease had renal failure[9]. Hypercalcaemic patients are more likely to have renal impairment (45%) than those with normocalcaemia (21%)[9]. Both of our patients with hypercalcaemia had renal impairment. Hypercalcaemia may reduce glomerular filtration rate, alter renal blood flow and precipitate within the renal tubules and renal interstitium to cause renal damage[10]. There is a positive correlation between Bence Jones proteinuria and renal failure[9,11,12]. The pathogenesis of renal damage in Bence Jones proteinuria is thought to be due to tubular dysfunction and is seen in proteinuria of > 1g/day[9]. Several studies have shown that total plasma exchange (TPE) is more effective than dialysis in removing Bence Jones proteins[13-15]. In one prospective trial[16], the majority of dialysis dependent patients recovered adequate renal function in 30 days after the start of TPE. Two-thirds of these patients survived one year, compared with less than one-third in the dialysis-only group. In our male patient (OKS), there was marked improvement in his renal function after 3 days of TPE.

Treatment response in Ig D myeloma patients is similar to other subtypes of myeloma[4] but the median duration of survival appears to be shorter (12-17 months)[2,3,17]. The Durie-Salmon staging of disease does not predict survival in Ig D myeloma patients[18] and response does not appear to correlate with the level

of paraprotein and renal function[17]. With more aggressive and intensive treatment, the median duration of survival can be improved and may be comparable to the other subtypes of myeloma[4]. A longer duration of survival was seen in Japanese patients with associated kappa light chain disease[3] but this was not reported in patients from the Mayo Clinic[4]. The best treatment results for myeloma are obtained with allogeneic bone marrow transplantation, with 35% of patients in complete remission after allografting[19,20]. This may be due to graft-versus-myeloma effect. However, transplant-related morbidity and mortality is much higher in allogeneic bone marrow transplantation. The procedure is also limited to a minority of patients, mainly of a younger age group. Autologous bone marrow transplantation may be an option in achieving greater tumour reduction and improving response rate, response duration and disease-free survival. Early transplant-related morbidity and mortality is much less (<5%) and this procedure can be extended to older age patients. Recently, autologous tandem transplantation has been shown to be a feasible procedure and has demonstrated to increase the rate of complete remission[21].

In summary, Ig D myeloma is a rare disease, accounting for only 2% of newly diagnosed myeloma. It should be considered if only a light chain band is detected on immunoelectrophoresis. Both lambda light chain paraproteinaemia and renal impairment are commoner in Ig D myeloma patients. These patients should be treated in a similar way as the other subtypes of myeloma with intensive combination chemotherapy. Autologous bone marrow transplantation or stem cell rescue should be performed in suitable patients as this results in a better disease-free survival. Allogeneic bone marrow transplantation should be considered if this is a feasible option as graft-versus-myeloma effect results in long-term complete remission.

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