Case Study – Multiple Myeloma

Significance of Results

The presented test findings strongly suggest a potential diagnosis of multiple myeloma in the patient under examination. This statement is supported by several clinical indicators. Notably, the patient's demographic profile, such as being a 71-year-old male, aligns with established risk factors associated with multiple myeloma development. Research indicates that males are 1.5 times more likely to be afflicted by multiple myeloma than females, with the average age of diagnosis being 69 years (Padala et al., 2021). Thus, the patient's age and gender place him within a demographic predisposed to multiple myeloma onset.

Moreover, the patient reported chest pain, prompting further investigation. Cardiac biomarkers, including creatine kinase (CK), were assessed, all yielding values within reference limits. Similarly, an electrocardiogram (ECG) revealed no abnormalities, effectively eliminating cardiac etiology as the source of the reported pain. Further, the possibility of a rib fracture was dismissed. Considering multiple myeloma's pathological mechanism, characterised by monoclonal plasma cell proliferation and paraprotein release, skeletal involvement leading to bone pain, particularly in regions such as the ribs and spine, is well-established (Koshiaris et al., 2018). Therefore, the patient's chest pain aligns with multiple myeloma-related skeletal manifestations.

Additionally, the patient's slightly elevated blood pressure and mild paraesthesia may be attributed to heightened plasma viscosity, a common feature in multiple myeloma cases. Notably, approximately 53% of multiple myeloma patients report symptoms such as tingling in the extremities (Ramsenthaler et al., 2016), while hypertension is prevalent in multiple myeloma populations (Chari et al., 2016).

Bone pain, a hallmark symptom encompassed by the "CRAB" diagnostic criteria for multiple myeloma (denoting hyperCalcaemia, Renal impairment, Anaemia, and Bone lesions), further supports the diagnostic hypothesis. Although the patient's

haematology results do not reveal anaemia, hypercalcemia is evident, likely stemming from bone degradation secondary to multiple myeloma-induced lesions (Koshiaris et al., 2018). Notably, a calcium level exceeding 2.75 mmol/L constitutes a myeloma-defining event, as stated in the British Journal of Haematology, potentially obviating the need for invasive procedures such as bone marrow biopsy (Sive et al., 2021). The renal function results, such as the GFR (glomerular filtration rate), showed no renal impairment, however given the presence of bone pain and hypercalcaemia, this isn't significant enough to rule out multiple myeloma.

The total protein and immunoglobulin profile results also suggest multiple myeloma. Due to the proliferation of immunoglobins, it is likely that the total protein level in serum is elevated in cases of multiple myeloma which it is in this case. Additionally, due to the proliferation being monoclonal, it is likely to also see an elevation in one type of immunoglobulin and a suppression in other types. This is also seen in this case as the patient has an elevated IgG result and little to no IgM and IgA (Gupta et al., 2020).

Gupta et al. (2020) explain that monoclonal paraproteins are indicators of multiple myeloma as they are the main product of the plasma cell proliferation. Serum protein electrophoresis is employed to identify these paraproteins by separating the proteins based on size and charge as they traverse a gel matrix (Chabrun et al., 2021). A photo of the result is shown in Figure 1. Notably, a distinct dark band observed in the gamma globulin region denotes the presence of a paraprotein, a characteristic finding in multiple myeloma diagnosis. It should also be noted that the patient has previously typed paraprotein persists which could indicate the presence of monoclonal gammopathy of undetermined significance (MGUS), an asymptomatic condition where paraproteins are formed. It is accepted that all cases of myeloma are preceded by this condition, although it is not normally diagnosed (Pfreundschuh, 2015).

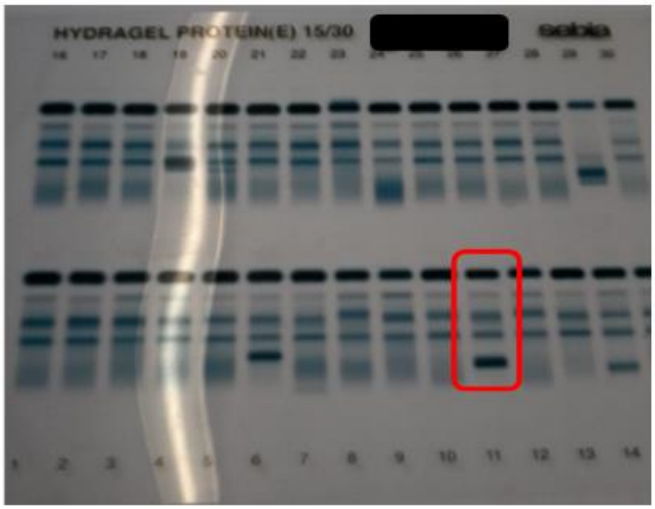

Figure 1: A photo showing the serum electrophoresis result of the patient marked with a red border.

Following this, serum immunofixation is performed to further distinguish which proteins are present in the patient sample. The result for the serum immunofixation is shown below in Figure 2.

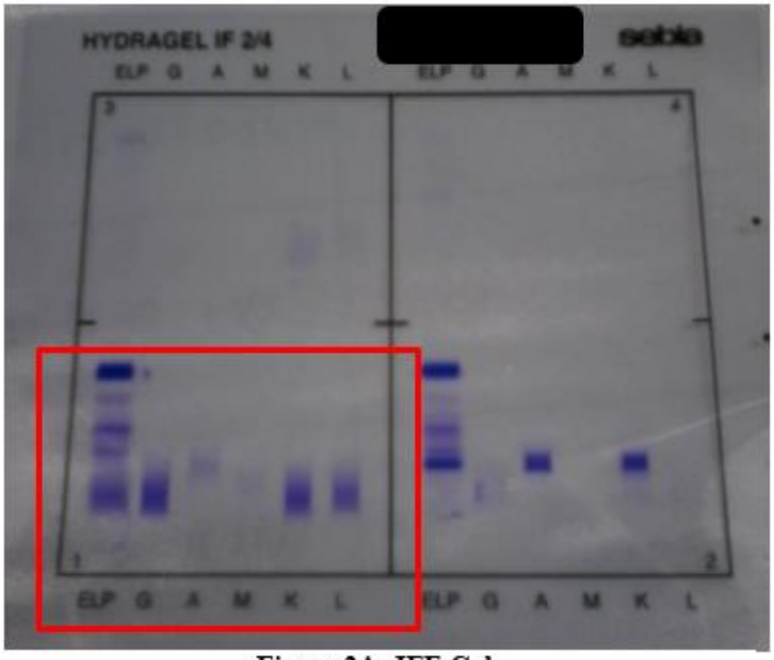

Figure 2A- IFE Gel

Figure 2: A photo showing the results of the serum immunofixation bordered with a red outline.

The interpretation of immunofixation gels, as illustrated by Wei et al. (2021), involves the addition of the sample to each lane. The initial lane represents standard gel electrophoresis and is expected to exhibit a pattern like the bands depicted in Figure 1. Subsequent lanes undergo treatment with antiserum specific to labelled proteins (IgG, IgA, IgM, kappa, and lambda). The presence of a paraprotein shows as a dark band in the first lane and subsequently in corresponding lanes. However, the absence of a dark band in the first lane, coupled with a dissimilar pattern compared to Figure 1, raises doubts regarding the accuracy of the immunofixation gel. Possible explanations include a testing error, such as sample misidentification. Moreover, the observed kappa and lambda bands within a typical ratio suggest a normal polyclonal response, as explained by Myeloma UK (2021).

The provided interpretation of the immunofixation results states that there is an increase in the IgG Kappa region as well as a slight increase in the lambda region. This supports the diagnosis of multiple myeloma by confirming the presence of a

monoclonal protein and further differentiates the condition into possible IgG Kappa myeloma.

A further test is undertaken for the presence of Bence Jones proteins. The results are shown in Figure 3 and show a dark band indicating the presence of Bence Jones proteins. These are immunoglobulin light chains and are regarded as tumour markers as they are found in excess in the urine in cases of multiple myeloma. They can also be present in cases of renal impairment, however, the renal function tests for this patient do not indicate this.

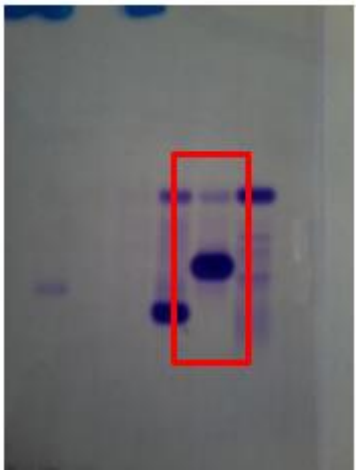

Figure 3: A photo showing the results of Bence Jones Protein electrophoresis.

In summary, the amalgamation of symptoms and laboratory findings strongly suggests the likelihood of multiple myeloma as a plausible diagnosis. Notably, the adherence to the CRAB criteria and the presence of paraprotein constitute significant diagnostic indicators. While consideration may be given to repeating the immunofixation assay to ensure result accuracy, the supplied evidence, particularly the presence of paraprotein and the occurrence of hypercalcemia, deemed a myeloma-defining event, provides sufficient grounds for diagnosis, showing how integral these tests are.

Treatments

There are certain factors that can impact what treatment options are available for the patient and which treatment is most beneficial for their condition.

Firstly, understanding the risk category for the patient is essential in deciding the best route to take with treatment. There are three stages of risk – standard, intermediate, and high risk. This can be determined by testing for a cytogenetic abnormality (Rajkumar & Kumar, 2016). Metaphase karyotyping or fluorescence in situ hybridisation (FISH) testing can be utilised to establish this (Rajan & Rajkumar, 2015). It can therefore be argued that these tests should be performed on the patient to ensure they are treated optimally. Table 1 shows possible cytogenetic abnormalities compared to their risk group as described by Rajkumar & Kumar (2016).

Table 1: A table to show cytogenetic abnormalities and their corresponding multiple myeloma risk groups as described by Rajkumar & Kumar (2016).

Cytogenetic Abnormality	Risk Group
Normal	Standard
t(11;14)	Standard
t(6;14)	Standard
Trisomies	Standard
t(4;14)	Intermediate
gain(1q)	Intermediate
t(14;16)	High
t(14;20)	High
del(17p)	High

Another pertinent consideration is the patient's suitability for autologous stem cell transplantation (ASCT). ASCT operates on the principle of harvesting haematopoietic stem cells (HSCs) from the patient, which can subsequently be reinfused following treatment to restore depleted supplies. This approach is advantageous, as high-dose treatments, such as chemotherapy, may target all HSCs, irrespective of their involvement in the disease process, potentially resulting in significant depletion if not

promptly countered (Balassa et al., 2019). Sive et al. (2021) explain that there is no definitive age criteria for ASCT eligibility, however, it is more commonly offered to patients under the age of 70. Despite this, patients over this age with little to no comorbidities can also be considered for this treatment. The renal and liver function tests, along with the cardiac markers, for this patient do not suggest the presence of comorbidities and, therefore, the patient may be considered for ASCT.

Considering these two factors, different standardised treatment pathways can be followed. These are shown in Figure 4 using information derived from Rajkumar & Kumar (2020).

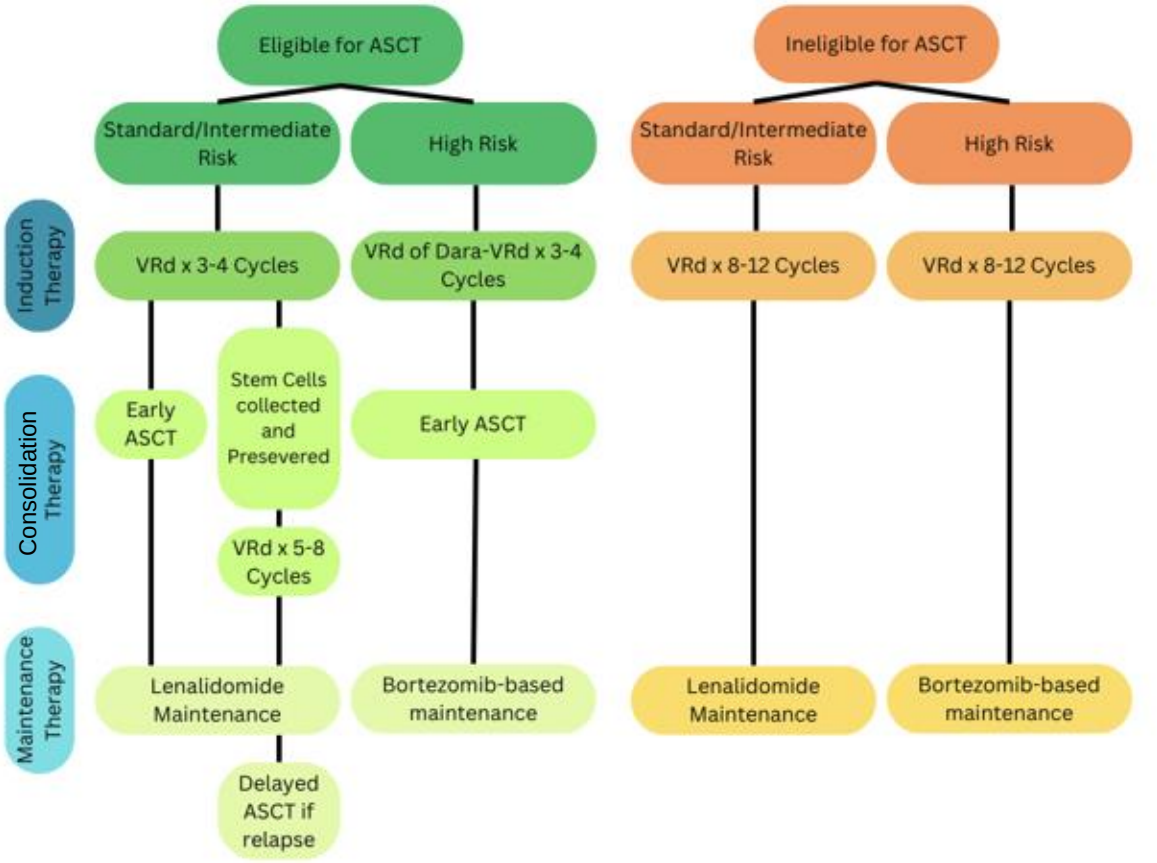

Figure 4: A chart stating the possible treatment routes for multiple myeloma using information derived from Rajkumar & Kumar (2020).

Rajkumar & Kumar (2020) explain that all patients are advised to undergo induction therapy, which involves multiple cycles of either VRd or Dara-VRd, depending on their eligibility. VRd is a three-drug regimen comprising bortezomib, lenalidomide, and the

corticosteroid dexamethasone, while Dara-VRd is a four-drug regimen that includes daratumumab in addition to the aforementioned drugs. Bortezomib, a proteasome inhibitor, induces apoptosis in myeloma cells by disrupting the degradation of proteins within proteasomes, resulting in the accumulation of toxic proteins and cellular stress (Teicher & Tomaszewski, 2015). Lenalidomide enhances T cell activity, promoting cell death, while suppressing pro-inflammatory cytokines that support myeloma cell growth, thereby inhibiting proliferation (Holstein & McCarthy, 2017). CD38 antigens are predominant in myeloma cells and daratumumab is used to target these using monoclonal antibodies that bind to them leading to cell death (Nooka et al., 2019).

During the next stage, consolidation therapy, the patient either undergoes ASCT or they continue a similar course to their induction therapy if illegible for ASCT (Rajkumar & Kumar, 2020).

This leads to the final stage- maintenance therapy. It is employed to prolong the period of disease control and aims to increase survival. Treatment is often taken over an extended period and, therefore, it is important that the drugs used are not overly toxic. Because of this, lenalidomide or bortezomib are often used as they are known to produce little side effects in comparison to other drugs (Lipe et al., 2016). If the patient relapses after this treatment, it is possible for more courses and ASCT to take place if stem cells were initially taken and persevered but not used (Rajkumar & Kumar, 2020).

There are many treatments that are currently being researched that may prove promising for treatment of multiple myeloma. Immunotherapy is one area that has shown encouraging developments, for example, research into the use of chimeric antigen receptor T-cells (CAR-T). These are engineered cells that can specifically target B cell maturation antigen (BCMA) – an antigen that is found only on plasma cells, some B cells, and multiple myeloma cells (Lin et al., 2019).

These cells were first reported in the late 1980's but were not successful in an in-human trial until 2010 where CAR-T cells were employed in the treatment of B cell lymphoma. The first preclinical report for CAR-T cells for the treatment of multiple myeloma was released in 2013 with in-human Phase 1 clinical trials beginning in 2016. By 2022, the product idecabtagene was approved by the FDA. In 2022,

ciltacabtagene, a similar product with the same mechanism of action, was approved. Ciltacabtagene proved slightly more effective with results showing a 97% overall response rate compared to 73% for idecabtagene. The HPRA and MHRA is yet to approve any CAR-T products and, therefore, they are not available for patients unless they are enrolled in a clinical trial (Gahvari et al., 2023).

There are many limitations to this method, such as the development of resistance to CAR-T cells by mechanisms such as antigen shedding, antigen escape, or CAR-T cell exhaustion (Manier et al., 2022). Additionally, many side effects have been noted such as cytokine release syndrome, immune cell-associate syndrome, and infectious complications. The list of side effects is expected to grow as trials continue and their significance compared to the benefits of the treatment will be assessed. CAR-T treatment also requires T cells to be collected from the patient using an apheresis machine. This may be difficult in causes of multiple myeloma as anaemia is common. Furthermore, once the T cells are collected, there will be a waiting period whilst they are modified where the patient would need to undergo bridging treatment (Gahvari et al., 2023). Some other treatments currently in clinical trials or at early stages of authorisation show means of administration that may be more accessible to patients such as Selinexor that is administered orally.

Selinexor is a selective inhibitor of nuclear export (SINE) that has been recently approved by the EMA but has not been fully approved by the MHRA. It is currently under conditional authorisation. It works by binding to the protein XPO1 and inhibiting its actions. XPO1 is a protein that exports proteins across the nuclear membrane. It is more prevalent in multiple myeloma cells as it transports tumour suppressor proteins in the cytoplasm where it becomes inactive. This allows the myeloma cells to grow and proliferate. By suppressing the XPO1 protein, the tumour suppressor proteins in the nucleus accumulate and initiate cell death (Huang et al., 2024).

Prognosis

Despite recent advancements, multiple myeloma remains to be an uncurable disease with all suffers succumbing to it (Hanbali et al., 2017). It is reported that multiple myeloma only accounts for 2% of cancer cases in the US but is responsible for >2% of cancer deaths (Padala et al., 2021). Although having a low survival rate, the time range for survivals varies depending on many factors.

It can be noted that early diagnosis is crucial in prolonged survival rates with figures showing that 84% of patients survive more than 5 years if diagnosed at an early stage compared to only 26% of patients who are diagnosed at a more advanced stage. Additionally, the 1-year survival rate for those referred by a GP is 70% compared to 42% of those referred through hospital admissions (Seesaghur et al., 2021). This is likely due to patients being admitted due to more severe symptoms, indicating more advanced progression of the disease. Using these figures for GP referrals along with the evidence from the blood tests that indicate no anaemia or renal impairment, it could be argued that the patient is more likely to survive more than 5 years.

Rajkumar (2020) describes that the median survival rate for multiple myeloma is approximately 6 years, however, in patients that received ASCT, the overall survival rate is approximately 8 years. The prognosis of this patient would therefore be impacted by the eligibility status for ASCT.

The cyto-genetics of the patient has also been shown to impact the prognosis. This is shown in table 2 using information derived from Rajkumar (2020). Therefore, this patient should undergo cytogenetic testing to understand the prognosis better.

Table 2: A table to show the median overall survival rates of different cytogenic abnormalities using information derived from Rajkumar (2020).

Cytogenetic Abnormality	Median Overall Survival (years)
Normal	7-10
Trisomies	7-10
t(11;14)	7-10
t(6;14)	7-10
t(4;14)	5
gain(1q)	5
t(14;16)	5
t(14;20)	5
del(17p)	5

The tumour burden, also known as staging, should be assessed to understand the patient's prognosis, with those at a higher stage receiving a poorer prognosis than the earlier stages. There are a variety of different methods to do so such as the revised international stage system, shown in Table 3 (Rajkumar, 2020).

Table 3: The revised international staging system for multiple myeloma (Rajkumar, 2020).

Stage	Observations
Stage I	• Serum Albumin ≥ 3.5g/dL • Serum beta-2-microglubin <3.5 mg/L • No high-risk cytogenetics • Normal serum lactate dehydrogenase
Stage II	• Not fitting stage I or III
Stage III	• Serum beta-2-microglobuin >5.5 mg/L • High risk cytogenetics OR elevated serum lactate dehydrogenase

The revised international stage system uses results for cytogenetics, serum beta-2-microglubin, and serum lactate dehydrogenase test- all of which were not tested. These would be needed to understand the stage of the disease. Despite this, the serum albumin result of 4.1g/dL indicate that the patient may be at stage I, meaning they may have a better prognosis.

In summary, this patient shows indications of suffering from stage I IgG kappa multiple myeloma. They do not show signs of anaemia or renal impairment but show symptoms that support indications of bone lesions. They are suffering from hypercalcaemia which is a myeloma defining event and show evidence of IgG Kappa paraprotein which further solidifies this diagnosis. Further testing and assessment of eligibility for ASCT should be reviewed to assess disease progression and provide the optimal treatment for a better prognosis.

Bibliography

- Balassa, K., Danby, R. and Rocha, V. (2019) 'Haematopoietic Stem Cell Transplants: Principles and indications', *British Journal of Hospital Medicine*, 80(1), pp. 33–39. doi:10.12968/hmed.2019.80.1.33.
- Chabrun, F. *et al.* (2021) 'Achieving expert-level interpretation of serum protein electrophoresis through deep learning driven by human reasoning', *Clinical Chemistry*, 67(10), pp. 1406–1414. doi:10.1093/clinchem/hvab133.
- Chari, A. *et al.* (2016) 'Incidence and risk of hypertension in patients newly treated for multiple myeloma: A retrospective cohort study', *BMC Cancer*, 16(1). doi:10.1186/s12885-016-2955-0.
- Gahvari, Z. *et al.* (2023) 'Update on the current and future use of CAR-T to treat multiple myeloma', *European Journal of Haematology*, 112(4), pp. 493–503. doi:10.1111/ejh.14145.
- Gupta, N., Sharma, Aparna and Sharma, Alpana (2020) 'Emerging biomarkers in multiple myeloma: A Review', *Clinica Chimica Acta*, 503, pp. 45–53. doi:10.1016/j.cca.2019.12.026.
- Hanbali, A. *et al.* (2017) 'The evolution of prognostic factors in multiple myeloma', *Advances in Hematology*, 2017, pp. 1–11. doi:10.1155/2017/4812637.
- Holstein, S.A. and McCarthy, P.L. (2017) 'Immunomodulatory drugs in multiple myeloma: Mechanisms of action and clinical experience', *Drugs*, 77(5), pp. 505–520. doi:10.1007/s40265-017-0689-1.
- Huang, Q. *et al.* (2024) 'Treatment of multiple myeloma with Selinexor: A Review', *Therapeutic Advances in Hematology*, 15. doi:10.1177/20406207231219442.
- Koshiaris, C. *et al.* (2018) 'Early detection of multiple myeloma in primary care using blood tests: A case–control study in Primary Care', *British Journal of General Practice*, 68(674). doi:10.3399/bjgp18x698357.
- Lin, Q. *et al.* (2019) 'Recent updates on car T clinical trials for multiple myeloma', *Molecular Cancer*, 18(1). doi:10.1186/s12943-019-1092-1.

- Lipe, B., Vukas, R. and Mikhael, J. (2016) 'The role of maintenance therapy in multiple myeloma', *Blood Cancer Journal*, 6(10). doi:10.1038/bcj.2016.89.
- Manier, S. *et al.* (2022) 'Current state and next-generation CAR-T cells in multiple myeloma', *Blood Reviews*, 54, p. 100929. doi:10.1016/j.blre.2022.100929.
- Myeloma UK (2021). Available at: https://www.myeloma.org.uk/wp-content/uploads/2023/08/Myeloma-MGUS-and-Related-Conditions-A-Guide-for-GPs.pdf (Accessed: 15 April 2024).
- Nooka, A.K. *et al.* (2019) 'Daratumumab in multiple myeloma', *Cancer*, 125(14), pp. 2364–2382. doi:10.1002/cncr.32065.
- Padala, S.A. *et al.* (2021) 'Epidemiology, staging, and management of multiple myeloma', *Medical Sciences*, 9(1), p. 3. doi:10.3390/medsci9010003.
- Pfreundschuh, M. (2015) 'Inheritance in MGUS and MM', *Oncotarget*, 6(32), pp. 32287–32288. doi:10.18632/oncotarget.5960.
- Rajan, A.M. and Rajkumar, S.V. (2015) 'Interpretation of cytogenetic results in multiple myeloma for clinical practice', *Blood Cancer Journal*, 5(10). doi:10.1038/bcj.2015.92.
- Rajkumar, S.V. (2020) 'Multiple myeloma: 2020 update on diagnosis, risk-stratification and management', *American Journal of Hematology*, 95(5), pp. 548–567. doi:10.1002/ajh.25791.
- Rajkumar, S.V. and Kumar, S. (2016) 'Multiple myeloma: Diagnosis and treatment', *Mayo Clinic Proceedings*, 91(1), pp. 101–119. doi:10.1016/j.mayocp.2015.11.007.
- Rajkumar, S.V. and Kumar, S. (2020) 'Multiple myeloma current treatment algorithms', *Blood Cancer Journal*, 10(9). doi:10.1038/s41408-020-00359-2.
- Ramsenthaler, C. *et al.* (2016) 'Prevalence of symptoms in patients with multiple myeloma: A systematic review and meta-analysis', *European Journal of Haematology*, 97(5), pp. 416–429. doi:10.1111/ejh.12790.
- Seesaghur, A. *et al.* (2021) 'Clinical features and diagnosis of multiple myeloma: A population-based cohort study in Primary Care', *BMJ Open*, 11(10). doi:10.1136/bmjopen-2021-052759.
- Sewpersad, S. and Pillay, T.S. (2020) 'Historical perspectives in clinical pathology: Bence Jones protein—early urine chemistry and the impact on

Modern Day Diagnostics', *Journal of Clinical Pathology*, 74(4), pp. 212–215. doi:10.1136/jclinpath-2020-206675.

- Sive, J. *et al.* (2021) 'Guidelines on the diagnosis, investigation and initial treatment of myeloma: A british society for Haematology/UK myeloma forum guideline', *British Journal of Haematology*, 193(2), pp. 245–268. doi:10.1111/bjh.17410.
- Teicher, B.A. and Tomaszewski, J.E. (2015) 'Proteasome inhibitors', *Biochemical Pharmacology*, 96(1), pp. 1–9. doi:10.1016/j.bcp.2015.04.008.
- Wei, X.-Y. *et al.* (2021) 'Deep collocative learning for immunofixation electrophoresis image analysis', *IEEE Transactions on Medical Imaging*, 40(7), pp. 1898–1910. doi:10.1109/tmi.2021.3068404.