Myelomatosis with the "a₂-Type" Serum Protein Pattern

By J. A. Owen and W. D. Rider

Patients with myelomatosis, whose electrophoretic serum protein patterns have contained a discrete component in the a₂-globulin fraction, have been described on very few occasions; moreover, not all of the reported cases have been universally accepted as instances of "a₂-type" myeloma protein. Indeed, Waldenström has questioned the existence of the "a₂-type" myeloma protein.

Wuhrmann and his co-workers, who were the first to describe this type of protein abnormality, reported that, in their cases, the course of the disease was particularly rapid. The prognostic importance of this finding, if confirmed, together with the rarity of this type of electrophoretic pattern, prompts this description of a further example which has been compared with previously reported cases.

Clinical and Laboratory Findings

The patient, a married woman 71 years old, was first seen in January 1955, complaining of pain in the chest. Radiological examination demonstrated multiple osteolytic areas in the ribs and also in the skull and pelvis; biopsy of sternal marrow revealed areas in which myeloma cells, mostly of the immature type (fig. 1), were present in large numbers. Other findings were: hemoglobin, 8.8 Gm./100 ml.; erythrocytes, 3.2 x 10⁹/mm.³; leukocytes, 3.8 x 10⁹/mm.³; platelets, 320 x 10⁹/mm.³; E.S.R., 140 mm./1 hr.; plasma proteins (sodium sulphite fractionation): "albumin," 3.2 Gm./100 ml.; "globulin," 3.7 Gm./100 ml. Paper electrophoresis revealed a considerable increase in a₂-globulin (fig. 2a); quantitative results are listed in table 1; blood urea nitrogen, 39 mg./100 ml.; serum cholesterol 184 mg./100 ml. The urine at this stage did not contain protein.

On immunological examination, for which we are indebted to Dr. L. Korngold, Sloan-Kettering Institute, the serum gave a reaction typical of "Group III" myeloma.

The patient was treated by means of oral urethane and nitrogen mustard (R 151) for 10 weeks, at the end of which therapy was discontinued because of leukopenia and nausea. The daily dose of urethane was 1 Gm. and the oral nitrogen mustard 50 mg. (R 151).

The patient remained reasonably well until January 1956, when she was given local x-ray therapy to dorsolumbar vertebrae on account of pain. Thereafter the patient's condition very gradually deteriorated.

In September 1956, proteinuria was first noticed. Some of the urinary protein was Bence Jones protein, being soluble at 100 C.; on electrophoresis two abnormal components were demonstrated, migrating as y-globulins, along with albumin and traces of other globulins (fig. 2b).

The patient's condition continued to deteriorate. She developed multiple pathological fractures and eventually died in March 1957. Autopsy revealed extensive deposits of myeloma tissue in sternum, ribs, skull, vertebrae and femur; histologically, these deposits

We are indebted to Dr. A. W. Wright for providing clinical details of the case described, and to Dr. L. N. Easson for organizing the collection of some of the blood and urine samples.

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Fig. 1.—Sternal marrow showing immature myeloma cells (x 1000).

consisted of sheets of myeloma cells. There was dilatation of the renal tubules which were filled with casts and which were, in some areas, necrotic. There was no evidence of amyloidosis or any other disease.

**DISCUSSION**

As Snapper et al. have pointed out, some authors have classified as "a₂-type" serum protein, patterns in which the a₂-globulin was only moderately increased. In the present discussion the term "a₂-type" serum protein pattern has been restricted to those in which the a₂-globulin fraction has constituted more than 20 per cent of the total protein, since it is more certain that such a change is due to the presence of myeloma protein rather than to the non-specific increase in a₂-globulin which occurs in many conditions, including neoplasia, collagen disease and infection.

Relatively high a₂-globulin peaks also occur in various renal disorders, notable in the nephrotic syndrome, possibly as a result of the relatively low renal clearance rates of this protein fraction. Thus, renal damage with proteinuria, which is often associated with myelomatosis, must be considered.

**TABLE 1.**—Serum Proteins

<table>
<thead>
<tr>
<th>DATE</th>
<th>TOTAL PROTEIN (Gm./100 ml)</th>
<th>ALBUMIN (%)</th>
<th>α₁- (%)</th>
<th>α₂- (%)</th>
<th>β (%)</th>
<th>γ-globulin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/3/55</td>
<td>7.4</td>
<td>39</td>
<td>3</td>
<td>43</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>23/4/55</td>
<td>8.3</td>
<td>42</td>
<td>2</td>
<td>39</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>27/1/56</td>
<td>7.1</td>
<td>35</td>
<td>4</td>
<td>42</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>29/5/56</td>
<td>7.4</td>
<td>41</td>
<td>4</td>
<td>36</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>8/9/56</td>
<td>6.1</td>
<td>40</td>
<td>7</td>
<td>40</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>25/9/56</td>
<td>6.5</td>
<td>30</td>
<td>5</td>
<td>51</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>25/10/56</td>
<td>7.3</td>
<td>30</td>
<td>4</td>
<td>53</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>
as a possible factor in the production of the "α₂-type" pattern. Reiner and Stern\textsuperscript{12} attributed an unusual electrophoretic pattern occurring in a patient with myelomatosis, and showing some increase in α₂-globulin, to renal damage. In another case described by Sandkühler\textsuperscript{11} (which, curiously, has been confused by both Snapper et al.\textsuperscript{8} and Waldenström\textsuperscript{1} with a patient having a true α₂-myeloma pattern and under the care of Dr. Sandkühler, but actually described by Wuhrmann et al.\textsuperscript{3}), the electrophoretic pattern (loc.cit. fig. 2) initially showed a strong peak in the γ-globulin region; later an elevation of the α₂-globulin was noted associated with marked increase in nonprotein nitrogen content of the serum. However, not all the cases which have been encountered with the "α₂-type" pattern have had proteinuria with poor renal function; moreover, a marked increase in serum α₂-globulin rarely occurs in patients whose serum contains a myeloma protein migrating in some other zone, even in the presence of marked renal impairment. This suggests strongly that the increase in α₂-globulin in the patterns termed "α₂-type" is due to the presence of a true myeloma protein and not a consequence of renal damage. Immunological examination of the serum in the present case supports this.

Various features of the reported cases of myelomatosis with the α₂-type serum protein pattern are listed in table 2. A few other instances, mostly isolated, of this abnormality have been reported,\textsuperscript{12,14-17} but these have not been included in table since their data are largely incomplete.

While the total number of cases which have been encountered with this protein pattern is admittedly small there is little to suggest from the available data that the clinical and laboratory features (apart from the serum proteins) are in any way distinct from those of cases showing other protein abnormalities. A similar conclusion has been reached by Reiner.\textsuperscript{18} Data in
### Table 2.—Data on Published Cases of Myelomatosis with "α₂-Type" Myeloma Protein  
(Data are, as far as ascertainable, relevant to the time at which diagnosis was made.)

<table>
<thead>
<tr>
<th>Author</th>
<th>Sex</th>
<th>Age (yr.)</th>
<th>Survival Time (mo.)</th>
<th>Total Protein (g/100 ml.)</th>
<th>α₂-Globulin (%)</th>
<th>Hb (g/100 ml.)</th>
<th>Blood Uric Acid (mg/100 ml.)</th>
<th>E.S.R. (mm/hr.)</th>
<th>Maximum Cell Type</th>
<th>Proteinuria</th>
<th>Renal Function</th>
<th>Bone-Jones Proteinaemia</th>
<th>Radio-logical Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wuhrmann et al.</td>
<td>M</td>
<td>40</td>
<td>(short)</td>
<td>6.1</td>
<td>23</td>
<td>12</td>
<td>7.0</td>
<td>70</td>
<td>Immature</td>
<td>+</td>
<td>--</td>
<td>--</td>
<td>+</td>
</tr>
<tr>
<td>Soulier</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>14.6</td>
<td>50</td>
<td>10</td>
<td>*</td>
<td>109</td>
<td>*</td>
<td>+</td>
<td>--</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Griffiths &amp;</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>7.7</td>
<td>26</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Brews</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>5.1</td>
<td>26</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lohman et al.</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>11.3</td>
<td>76</td>
<td>*</td>
<td>*</td>
<td>188</td>
<td>*</td>
<td>+</td>
<td>--</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Kalpainen</td>
<td>M</td>
<td>56</td>
<td>9</td>
<td>8.8</td>
<td>39</td>
<td>*</td>
<td>7.1</td>
<td>148</td>
<td>*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M</td>
<td>56</td>
<td>*</td>
<td>*</td>
<td>7.6</td>
<td>24</td>
<td>12</td>
<td>4.7</td>
<td>85.11</td>
<td>*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Snapper et al.</td>
<td>F</td>
<td>65</td>
<td>4</td>
<td>8.7</td>
<td>68</td>
<td>10</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>F</td>
<td>8</td>
<td>89</td>
<td>10.3</td>
<td>75 (low)</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M</td>
<td>69</td>
<td>59</td>
<td>8.5</td>
<td>39</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Present Authors</td>
<td>F</td>
<td>71</td>
<td>24</td>
<td>7.4</td>
<td>43</td>
<td>10</td>
<td>9.6</td>
<td>109</td>
<td>Immature</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

1From time of diagnosis.
2This case was under the care of Dr. Sandkuhler.
3Values two years after diagnosis—initial findings normal.
4Also report a case with 19.2% α₂-globulin without further details.
5Data not recorded.
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Table 3 indicates, also, that there is little tendency in myelomatosis for any of the other protein patterns to be associated with particular clinical or laboratory features, as has been previously noted. Exceptions to this are the association of low sedimentation rates with minor protein changes and, possibly, the tendency for Bence Jones proteinuria to be less commonly associated with the "y-type" protein pattern.

In the majority of the reported cases with the a2-type pattern (as defined above) the myeloma cells have been immature in character. However, the number of reported cases is too small to permit the conclusion that a definite association is present. Considering chiefly other protein patterns, various authors concluded that there was no correlation between cell type and protein pattern, and this has been the experience of the present authors. However, others have concluded to the contrary. Obviously, further investigation of this point is required.

As far as prognosis is concerned, the rapid course of the disease noted in the cases with the a2-type pattern by Wuhrmann et al. has not been a constant feature of cases subsequently described. Wuhrmann et al., however, regarded as a2-type, patterns in which the a2-globulin level was only slightly elevated, possibly as a result of renal damage which would tend to influence the prognosis unfavorably. On the other hand, the association of immaturity of cell type and poor prognosis noted by these authors has also been observed by Bayrd (1948), although the occurrence of cases in which this association is lacking as it is in the present case, reduces the prognostic values of these observations.

In practice the a2-myeloma pattern is most likely to be confused with the nephrotic serum protein pattern. However, the nephrotic syndrome is usually associated with markedly reduced total serum protein concentration which helps in distinguishing between this condition and myelomatosis with the a2-type pattern and proteinuria. In the present case the serum cholesterol level was normal, which suggests that the estimation of serum cholesterol may also be of value in distinguishing between myelomatosis and the nephrotic syndrome, in which hypercholesterolaemia is usual. Knedel (1955), however, has reported one case of myelomatosis with the a2-type pattern in which lipemia was present, although the serum cholesterol level was not stated.

A considerable increase in a2-globulin occurs rarely in reticulosis. Hutchinson reported such a finding in a case of lymphoid reticulosis, possibly an example of macroglobulinaemia, and one of the authors has observed a case of giant follicular-cell lymphoma in which the serum a2-globulin constituted over 40 per cent of the total serum protein.

Summary

1. A case of myelomatosis with "a2-type" myeloma protein in the serum is described.
2. Previously reported cases of myelomatosis with this rare type of serum protein pattern have been reviewed.
3. It is concluded from the limited data available that the clinical features
### Table 3.—Findings in Myelomatosis According to Serum Protein Pattern

(Data are relevant (at least in the authors cases) to the time at which diagnosis was made and are expressed as incident (%) or as means ± standard error.)

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Source of Data</th>
<th>No.</th>
<th>Males (%)</th>
<th>Age (Yr.)</th>
<th>Total Serum Protein (Gm./100 ml.)</th>
<th>Proteinuria (%)</th>
<th>Bence Jones Proteinuria (%)</th>
<th>Radiological Bone Changes (%)</th>
<th>Survival Time* (mo.)</th>
<th>Hb. Gm./100 ml.</th>
<th>E.S.R. mm./hr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>α₂-Type</td>
<td>Literature (Table 2)</td>
<td>12</td>
<td>45</td>
<td>55 ± 4</td>
<td>8.7 ± 0.8</td>
<td>66</td>
<td>40</td>
<td>91</td>
<td>17 (5)</td>
<td>10.1 ± 0.6</td>
<td>119 ± 16</td>
</tr>
<tr>
<td>β-Type</td>
<td>Present</td>
<td>6</td>
<td>67</td>
<td>61 ± 1</td>
<td>9.7 ± 0.8</td>
<td>83</td>
<td>67</td>
<td>67</td>
<td>5 (4)</td>
<td>9.2 ± 0.8</td>
<td>125 ± 10</td>
</tr>
<tr>
<td>Fast γ-Type</td>
<td>Authors</td>
<td>14</td>
<td>64</td>
<td>66 ± 2</td>
<td>8.5 ± 0.4</td>
<td>60</td>
<td>14</td>
<td>72</td>
<td>12 (10)</td>
<td>10.9 ± 0.5</td>
<td>100 ± 8</td>
</tr>
<tr>
<td>Slow γ-Type</td>
<td>(Unpublished data)</td>
<td>20</td>
<td>55</td>
<td>64 ± 5</td>
<td>8.8 ± 0.6</td>
<td>75</td>
<td>20</td>
<td>85</td>
<td>9 (12)</td>
<td>10.9 ± 0.6</td>
<td>89 ± 8</td>
</tr>
<tr>
<td>Minor Abnormality</td>
<td></td>
<td>10</td>
<td>60</td>
<td>60 ± 4</td>
<td>6.1 ± 0.2</td>
<td>90</td>
<td>33</td>
<td>90</td>
<td>9 (4)</td>
<td>9.2 ± 1.5</td>
<td>41 ± 14</td>
</tr>
</tbody>
</table>

*From the time of diagnosis; number of cases in parenthesis.
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of cases with the “a2-type” serum protein pattern and the prognosis are, in general, not different from those of patients with other protein abnormalities.

**Summario in Interlingua**

1. Es describite un caso de myelomatosis con sero continente proteina myelomatoide “tipo a2.”
2. Es passate in revista le previemente reportate casos de myelomatosis con iste infrequente typo de configuration del proteina seral.
3. Super le base del limitate datos disponibile, le conclusion es formulate que le aspectos clinic e le prognose de casos con la configuration de proteina seral “tipo a2” non difere, in general, ab illos de patientes con altere anormalitates proteinic.

**REFERENCES**

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