Mast cells in parathyroid glands of hyperparathyroidism

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SYNOPSIS  Parathyroid glands from cases of hyperparathyroidism have been examined with particular attention to mast cells. In 'normal' glands accompanying an adenoma they were common, although there was a wide range in their frequency, whereas in pathological tissue, both adenoma and hyperplasia, mast cells were scarce. This difference between glands was examined with respect to alterations in gland size, to variations in the amount of interstitial tissue, to degrees of overactivity, and to anatomical development of the glands. No conclusions can be drawn with regard to the significance of mast cells in parathyroid tissue.

Since the recognition of primary chief cell hyperplasia as an entity (Cope, Keynes, Roth, and Castleman, 1958) the clear differentiation between adenoma and hyperplasia in some cases of hyperparathyroidism is generally acknowledged to be difficult. This occurs because of the inability to establish clear limits of histological normality in relation to function of parathyroid tissue. Comparative studies of normal and hyperactive human parathyroid tissue (Roth and Munger, 1962; Weymouth and Sheridan, 1966; Black, 1969; Faccini, 1970) have concentrated on histological and ultrastructural differences in the parenchymal cell forms. The mast cell, which was noted in parathyroid glands by Erdheim (1903) and described in the histology of normal human parathyroids (Morgan, 1936; Gilmour, 1939), has not been the subject of a comparative study. Particular attention has been given, therefore, to mast cells in parathyroidectomy material submitted between 1962 and 1972 to the Department of Pathology, Aberdeen Royal Infirmary. The opportunity to compare pathological and non-pathological tissue arises because of the routine surgical practice to examine histologically all glands identified at exploration. A quantitative analysis for mast cells has demonstrated a difference between glands which is discussed in this paper.

Materials and Methods

CASE SELECTION
Material from 56 cases of parathyroid exploration was reviewed (table I). All cases had undergone exploration as examples of primary hyperparathyroidism except one case of hyperplasia secondary to phosphaturic nephropathy. In 40 cases with three or more glands a definitive diagnosis of adenoma or hyperplasia was made according to the criteria of table II, and in 29 of these suitable material was available for further study. The separate categories into which the tissue from these cases was placed are given in table III.

<table>
<thead>
<tr>
<th>Number of cases reviewed</th>
<th>56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>29</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>11</td>
</tr>
<tr>
<td>1Uncertain but pathological</td>
<td>16</td>
</tr>
</tbody>
</table>

Table I  Histological diagnosis in cases of hyperparathyroidism
1Includes cases with only one gland.

<table>
<thead>
<tr>
<th>Adenoma</th>
<th>Hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of abnormal glands</td>
<td>Usually only 1</td>
</tr>
<tr>
<td>No. of nodules per gland</td>
<td>Usually only 1</td>
</tr>
<tr>
<td>Peripheral rim 'normal'</td>
<td>Present</td>
</tr>
<tr>
<td>Cell pleomorphism</td>
<td>Present</td>
</tr>
<tr>
<td>Cell type</td>
<td>Uniform</td>
</tr>
</tbody>
</table>

Table II  Criteria for separation of adenoma from hyperplasia

METACHROMATIC STAINS
Routine paraffin blocks were used to prepare three step sections of each gland to be stained for mast cells with Azure A according to Hughesdon (1949). This method, which permits permanently mounted...
Table III  Histological classification of tissue samples

<table>
<thead>
<tr>
<th>Categories of Tissue</th>
<th>No. Cases</th>
<th>No. Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>'Normal' rim adjacent to adenoma</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>'Normal' gland accompanying adenoma</td>
<td>21</td>
<td>58</td>
</tr>
<tr>
<td>Adenoma</td>
<td>8</td>
<td>32</td>
</tr>
</tbody>
</table>

The mast cells, whether present as a 'rim' adjacent to an adenoma or as a separate gland, was greater and in each instance the difference from pathological tissue was highly significant (p < 0.001).

Also, a comparison between pathological and 'normal' tissue was made with respect to the distribution of mast cells by site. The ratio of peripheral and central mast cell values for glands in each classified group is given in Table IV. A peripheral localization of mast cells predominates in pathological tissue, either adenoma or hyperplasia, which differs highly significantly (p < 0.001) from 'normal'.
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showed a considerable range which overlapped with that of pathological tissue. Indeed, in two adenoma
cases all ‘normal’ tissue showed values within the
‘adenoma’ range. In the examination of this dif-
ference between glands consideration was given to
four variables: the degree of pathological tissue
overactivity; variation in amount of interstitial
tissue; difference in ‘normal’ gland size; anatomical
relationship of glands.

Serum parathormone levels were not assayed in
these cases, but less precise indices of activity are
given by the level of hypercalcaemia and by the weight
of pathological tissue. In 11 cases an immediate pre-
operative serum calcium was available (corrected for
total serum protein) and in five cases there was a
record of accurate gland weights. In neither instance
was any correlation demonstrated between these
estimates and mast cell density in ‘normal’ glands
(highest or average value).

In 25 ‘normal’ glands from nine cases, taken over
the observed range of mast cell values, the amount of
interstitial tissue varied from 15 to 75%. Also, an
approximation of gland biopsy size was estimated
from the total area of sections. However, in neither
instance was any correlation evident when mast cell
values were plotted as a function of these estimates.

Table V gives the values for mast cells in glands of
the adenoma cases for which tissue from three
‘normal’ glands was submitted. They are arranged to
accentuate the unusual distribution of mast cells
amongst the glands. In most cases two ‘normal’
glands showed numbers which approximated, whilst
the third had almost twice as many mast cells. Tests
of significance for this observation have not proved
practicable. However, because of the embryological
relationship between glands as pairs, the anatomical
relationship between the adenoma and its corre-
sponding gland with the highest value was examined
by reference to the pathological records. No con-
sistent pattern of anatomical relationship was
displayed.

Discussion

It is clear from the results of this analysis that a dif-
ference exists with respect to the number of mast
cells in sections of parathyroid glands from cases of
hyperparathyroidism. Yet the difference is not

Table IV  Comparison of mast cell distribution by site

<table>
<thead>
<tr>
<th>Histological Diagnosis (No. of Glands)</th>
<th>Mast Cells per Field Ratio: Periphery$^a$ Centre (± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Normal’ (20)</td>
<td>1.28 (± 0.11)</td>
</tr>
<tr>
<td>Adenoma (21)</td>
<td>2.34 (± 0.42)</td>
</tr>
<tr>
<td>Hyperplasia (21)</td>
<td>3.65 (± 0.74)</td>
</tr>
</tbody>
</table>

Table V  Mast cell values of different glands in cases of adenoma

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Mast Cells per Field in Adenomas with Values of the Accompanying Gland Arranged in Order of Ascending Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pathological ‘Normal’ Adenoma</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Mean (±SEM)</td>
<td>0.50 ± 0.09</td>
</tr>
</tbody>
</table>

absolute (fig 1, table IV) and it cannot be concluded
that the mast cell patterns in the glands is charac-
teristic according to histopathological diagnosis or even
that it allows clear distinction between adenoma and
hyperplasia. No explanation can be given for those
adenoma cases for which all glands gave mast cell
values within the general pathological range (less
than 2 per field, table V). Nevertheless in the present
state of uncertainty regarding the pathogenesis of
primary hyperparathyroidism any factor which per-
mits separate classification of cases deserves
attention. Furthermore, these observations may have
practical value to the pathologist requested to dis-
tinguish between adenoma and hyperplasia on the
basis of light microscope examination of limited
tissue samples, since a gland showing more than two
mast cells per field (as defined) is unlikely to be
pathological.

The difference between glands that has been
demonstrated here raises two issues. Why are mast
cells less frequent in pathological tissue; conversely,
why does the frequency of their occurrence in
‘normal’ glands extend over such a range? It should
be emphasized that alterations in three-dimensional
structure have not been allowed for in the present
comparisons of mast cell numbers. Although the
results of table IV could be interpreted to indicate
change in distribution due to expansile growth of
tissue there was no evidence to support this from
analysis of other data. Furthermore, despite the
inaccuracies of the present estimates of gland size
from a biopsy, there is no indication that differences

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in amounts of interstitial tissue account for the variation amongst 'normal' glands, thus making it unlikely that the infrequency of mast cells in pathological tissue can be explained on the basis of lack of interstitial tissue in these glands. Also there is no evidence from the present study that mast cells provide an index of relationship between glands on the basis of development or activity. The role of mast cells in parathyroid glands is not understood.

In the context of mast cells and endocrine tissue, experimental animal studies (Clayton and Szego, 1967; Clayton and Masuoka, 1968; Melander and Sundler, 1972) have associated thyroid mast cell changes with alterations in thyroid hormone secretion in response to trophic hormone stimulation (TSH). However, species differences in characteristics of mast cell ultrastructure and amine precursor metabolism (Nunez and Gershon, 1973) have introduced doubts about the general applicability of these experiments to the human situation.

Despite these dissimilarities, emphasis may still be given to the association between mast cells and tissue stimulation by a trophic factor. Such an association requires investigation in other paired endocrine organs, such as the adrenal glands. Although no trophic substance has been demonstrated for the parathyroids, such a possibility requires re-examination, more particularly in view of the controversy over the proposed interrelationships between the parathyroids and kidneys in the regulation of vitamin D metabolism (Garabedian, Holick, DeLuca, and Boyle, 1972; Larkins, MacAuley, Colston, Evans, Galante, and MacIntyre, 1973).

A quantitative analysis of mast cells in parathyroid glands of hyperparathyroidism has demonstrated a significant difference between pathological and non-pathological tissue. However, clear discrimination between adenoma and hyperplasia has not been achieved, and no satisfactory explanation has been found to account for the variation between the non-pathological glands. An investigation of necropsy material is in progress to determine the distribution and variation of mast cell numbers in parathyroid glands of cases without evidence of altered calcium metabolism.

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References