Tyrosine-rich crystalloids in vocal cord mucosa

The presence of tyrosine-rich crystalloids in salivary neoplasms is well known, but such crystals have rarely been described in other sites. To our knowledge, the presence of tyrosine-rich crystals in vocal cord mucosa has not been previously described.

A 61-year-old man presented with hoarseness of voice for 12 months. He also complained of coughing, which had improved after he had stopped smoking. There was no history of any treatment to the vocal cords. His medical history included hypertension, anxiety, vasectomy and tonsillectomy. Microlaryngoscopy revealed Reinke’s oedema of the right vocal cord and a polyp of the left true vocal cord, which was removed. An H&E-stained section showed normal non-keratinising squamous epithelium covering oedematous vocal cord mucosa with focal fibroblastic proliferation. Scattered morular crystalline structures were present in the fibrous tissue arranged in the form of rosettes staining pink (fig 1A). There was no staining with periodic acid–Schiff, and the crystals were not birefringent. The diazotisation coupling method for tyrosine was positive in the crystals. When sections were stained with Millon’s stain, the crystals were red-brown (fig 1B).

“Tyrosine crystals” in a pleomorphic salivary adenoma were first reported by Bullock1 in 1953, and were identified on the basis of their crystalline appearance and positive staining with Millon’s reagent, which produces a red colour in the presence of phenols. Similar crystalline structures were subsequently identified in several pleomorphic adenomas of the parotid by Chaplin et al,2 who found the structures to include tryptophan, arginine and thiol groups, as well as tyrosine, and regarded them as “tyrosine-rich crystals”. The term “tyrosine-rich crystalloids” was preferred by Gould et al,3 who showed by electron microscopy that these crystal structures were finely granular and electron-dense but not birefringent and without a solid internal structure. The incidence of tyrosine-rich crystalloids has been reported to be 1.5–2% of salivary gland tumours. Some authors have attributed this range to the disparities in incidence among different racial groups. In a large series from Malawi, tyrosine crystals were observed in 24 of 113 cases of pleomorphic adenoma.1 It was speculated that the higher incidence in black patients may be a consequence of the role of tyrosine in pigment metabolism. This conjecture does not explain why the crystals are preferentially localised in pleomorphic adenoma. Tumours with such crystalloids do not appear to have higher concentrations of tyrosine than do those without. Moreover, these crystalloids are not seen in the tissues of patients with tyrosinosis, and excess administration of tyrosine to rats does not result in crystalloid deposition.4

The formation of tyrosine crystalloids in oncocytic cysts has been described.5 It was thought that the crystals formed in the epithelial cells lining the cyst and were then either excreted or accumulated after exfoliation and disintegration of the lining cells. Our case is unusual in presenting in the vocal cord. To our knowledge, this is the first reported case in that site. The possible explanations for this unusual finding are not clear, but we suggest a ruptured oxyphil cyst that resulted in the formation of an inflammatory polyp. Follow-up of the patient in clinic revealed improvement in his voice with some mild Reinke’s oedema of both vocal cords.

We report this case to highlight the existence of tyrosine crystals in this unusual site.

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REFERENCES

The oestrogen receptor-negative/progesterone receptor-positive breast tumour: a biological entity or a technical artefact?

A recent study by Rakha et al5 shows that breast tumours with single hormonal receptor positivity are biologically and clinically distinct groups and particularly that oestrogen receptor (ER)–negative/progesterone receptor (PR)–positive tumours exhibit more aggressive behavioural characteristics than double-receptor-positive tumours. However, there is also an increasingly prevalent opinion, that the ER−/PR+ phenotype does not exist and that the ER-negativity in these cases is due to inadequate tissue fixation or technical failure of the immunohistochemical assay.2–4

This is an important dichotomy to resolve because, if ER−/PR+ tumours simply represent an artefact of the method of assessment, then they are essentially positive for both the receptors, which may have implications for how these patients are managed. To investigate this, we reviewed data from a previous study, in which we had accumulated data on ER/PR phenotype expression in a large cohort of patients tested in 42 laboratories.5 In this study of 4053 breast tumours, a sizeable number (n = 131) were of the ER−/PR+ phenotype, which, unlike other studies with lower numbers of cases, allowed us to statistically test the distribution of this phenotype in stratified age groupings (table 1). We found that the ER−/PR+ phenotype occurs over twice as often in the <51-year patient age group as it does in the >50-year patient age group (table 2 and fig 1). This suggests that the ER−/PR+ phenotype is a biological entity. To further validate this possibility and exclude any methodological factor, we restricted the analysis to those results achieved from 16 laboratories that were proven to have reliable immunohistochemical assays of high sensitivity, because of their optimal performance in a national quality-assurance programme.9 These laboratories used antibodies and reagents similar to, and in some cases identical with,
Table 1  Oestrogen receptor (ER) and progesterone receptor (PR) status of 4053 invasive breast carcinomas with respect to patient age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>ER-ve, PR+ve</th>
<th>ER-ve, PR-ve</th>
<th>ER+ve, PR-ve</th>
<th>ER+ve, PR+ve</th>
<th>Total in each age group</th>
</tr>
</thead>
<tbody>
<tr>
<td>21–30</td>
<td>18 (45.0)</td>
<td>17 (42.5)</td>
<td>3 (7.5)</td>
<td>2 (5.0)</td>
<td>40 (1.0)</td>
</tr>
<tr>
<td>31–40</td>
<td>134 (45.9)</td>
<td>97 (33.2)</td>
<td>45 (15.4)</td>
<td>16 (5.5)</td>
<td>292 (7.2)</td>
</tr>
<tr>
<td>41–45</td>
<td>195 (57.9)</td>
<td>88 (26.1)</td>
<td>35 (10.4)</td>
<td>19 (5.6)</td>
<td>337 (8.3)</td>
</tr>
<tr>
<td>46–50</td>
<td>319 (58.6)</td>
<td>116 (21.3)</td>
<td>83 (15.3)</td>
<td>26 (4.8)</td>
<td>544 (13.4)</td>
</tr>
<tr>
<td>51–55</td>
<td>278 (53.5)</td>
<td>114 (21.9)</td>
<td>112 (21.5)</td>
<td>16 (3.1)</td>
<td>520 (12.8)</td>
</tr>
<tr>
<td>56–60</td>
<td>239 (51.0)</td>
<td>102 (21.8)</td>
<td>113 (23.1)</td>
<td>8 (1.6)</td>
<td>490 (12.1)</td>
</tr>
<tr>
<td>61–65</td>
<td>271 (55.3)</td>
<td>98 (20.0)</td>
<td>113 (23.1)</td>
<td>8 (1.6)</td>
<td>490 (12.1)</td>
</tr>
<tr>
<td>66–70</td>
<td>251 (57.2)</td>
<td>85 (19.4)</td>
<td>94 (21.4)</td>
<td>9 (2.1)</td>
<td>439 (10.8)</td>
</tr>
<tr>
<td>71–75</td>
<td>194 (57.6)</td>
<td>60 (17.8)</td>
<td>76 (22.6)</td>
<td>7 (2.1)</td>
<td>337 (8.3)</td>
</tr>
<tr>
<td>&gt;75</td>
<td>323 (55.1)</td>
<td>119 (20.3)</td>
<td>132 (22.5)</td>
<td>12 (2.1)</td>
<td>596 (14.5)</td>
</tr>
</tbody>
</table>

Total (receptor status) 2222 (54.8) 896 (22.1) 804 (19.8) 131 (3.2) 4053 (100)

Values are number (%).

Table 2  Frequency of invasive breast tumours with the oestrogen receptor (ER)-negative/progesterone receptor (PR)-positive phenotype in patients of ≤51 years and >50 years of age, in 4053 cases (a) and in a subset of 1865 tumours from laboratories shown to have high assay sensitivity for ER and PR (b)

<table>
<thead>
<tr>
<th>Series</th>
<th>Mean frequency (%)</th>
<th>p Value Mann-Whitney U test Two-tailed</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) 4053 tumours</td>
<td>131 (5.2 (95% CI 4.6 to 5.8)</td>
<td>2.4 (95% CI 1.7 to 3.1)</td>
</tr>
<tr>
<td>(b) 1865 tumours</td>
<td>57 (5.0 (95% CI 4.4 to 5.5)</td>
<td>2.1 (95% CI 1.4 to 2.8)</td>
</tr>
</tbody>
</table>

Figure 1  Mean frequency of occurrence of invasive breast tumours with the oestrogen receptor (ER)-negative/progesterone (PR)-positive phenotype in patients of ≤51 years and >50 years of age. (A) A series of 4053 breast tumours from 42 laboratories; (B) a sub-series of 1865 breast tumours from 16 laboratories with high assay sensitivity for ER and PR.

The results proved very similar to those derived from the full set of data; with the ER-+/PR+ phenotype occurring twice as often in the ≤51-year age group as in the >50-year age group (fig 1 and table 2). It appears therefore that the ER-+/PR+ breast carcinoma represents a distinct biological phenotype; if it were not and it was due to false-negative ER results caused by technical failure, as purported by De Maeyer et al and Nadji, the phenotype would occur with random frequency across all age groups.

We appreciate that the cut-off points that define a positive and negative result for ER and PR have lowered in recent years, in some instances to one in which as few as 1% of receptors present are considered to be a positive result, with respect to the patients likely response to hormonal therapy. In addition, a recent study by Dabbs et al has clearly demonstrated that, even when using optimally fixed tissues and any level of nuclear immunohistochemical staining of invasive tumour cells as a positive result, the ER-+/PR+ phenotype is still retained as an entity in ~5% of breast tumours. These studies taken together provide further evidence that ER-+/PR+ is not an artefact of fixation or due to the use of a lower threshold to define ER positivity.

The evidence presented confirms that there is undetectable expression of ER in the tumours of at least a small proportion (2–5%) of patients with breast cancer who have relatively high levels of PR expression. In addition, it shows that the ER-+/PR+ phenotype occurs on average twice as often in relatively younger patients (<51 years). These findings, taken together with the fact that these patients have worse outcomes than unequivocal double-receptor-positive cases, clearly indicate the need to test all ER- tumours for their PR status even though the ER-+/PR+ phenotype overall represents a small proportion of all breast cancers.

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7. Dabbs DJ, Carter GJ, Bhargava R. Fixation issues with breast carcinoma hormone receptors: ER negative PR positive carcinomas exist even with optimal fixation methods. 97th Annual USCAP Meeting 1–7 March 2008;27A.