Increased serum concentrations of type IV collagen and laminin associated with granulosa cell tumour of the ovary

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Abstract
A 65 year old woman presented with an ovarian mass. Ultrasonography and computed tomography findings, and an increased serum oestrogen concentration were suggestive of an oestrogen producing ovarian tumour. The tumour was removed surgically and weighed 460 g. The pathological diagnosis was adult-type granulosa cell tumour. Strong immunohistochemical staining specific for type IV collagen and laminin was observed, and these components were localised to the pericellular region of the granulosa cells. The serum concentrations of these basement membrane components (measured by radioimmunoassay) were very high before surgery, but decreased rapidly thereafter. Serial measurement of type IV collagen and laminin, in conjunction with other tumour markers and oestrogen concentrations, might be helpful in evaluating prognosis of ovarian granulosa cell tumours, in detecting metastatic or recurrent lesions and in monitoring response to treatment.

Keywords: granulosa cell tumour; type IV collagen; laminin.

Granulosa cell tumours of the ovary consist of neoplastic cell nests that contain many microfollicles, which resemble the normal granulosa cell layer with Call-Exner bodies. Neoplastic cells are arranged in a rosette in the microfollicles. Electron microscopy studies have suggested that the microfollicles contain the basement membrane components. The basement membrane consists of type IV collagen, laminin and heparan sulphate. To our knowledge, there have been no reports on serum concentrations of basement membrane components, such as type IV collagen and laminin, in patients with granulosa cell tumour of ovary. In the present study, we measured the circulating concentrations of type IV collagen and laminin in a patient with a granulosa cell tumour using specific radioimmunoassays for 7S collagen and the P-1 fragment of laminin.

Case report
In 1995, a 65 year old postmenopausal woman attended the Department of Obstetrics and Gynaecology at Wakayama Medical College. She complained of discomfort in the lower abdomen and vaginal bleeding. A vaginal smear test showed numerous keratinised, epithelial cells, indicating an oestrogenic effect. Exploratory dilation and curettage revealed endometrial hyperplasia. The serum concentration of CA125, an ovarian tumour marker, was 215 U/ml. Serum follicle stimulating hormone (FSH), luteinising hormone (LH), and oestradiol (E2) concentrations (measured by radioimmunoassay) were, respectively, 0.2 IU/l, 2.0 IU/l and 111 ng/ml.

Ultrasonography revealed a multilobular cystic mass 10 cm in diameter with heterogeneous echogenicity in the pelvic region. A computed tomography (CT) scan confirmed the presence of a heterogeneous tumour in the pelvis. No metastases were found. Surgical exploration revealed an encapsulated ovarian tumour, which was removed after careful dissection from the surrounding tissue. The tumour was confined to the ovary. It had a smooth surface covered by a capsule and was largely spherical, measuring 10 × 6 × 5 cm, and weighed 460 g. The cut surfaces of the tumour revealed multiple cysts with areas of haemorrhage and necrosis. The pathological diagnosis was adult-type granulosa cell tumour (fig 1A), with a mixed microfollicular and trabecular pattern. Serum FSH, LH, and E2 concentrations returned to the postmenopausal range (112 IU/l, 76 IU/l, and <25 ng/ml, respectively) 45 days after surgery.

Methods
A specific mouse monoclonal antibody directed against human type IV collagen was produced in our laboratory and a specific polyclonal antibody raised in rabbits against human laminin was purchased from Fuji Chemical Co (Toyama). Localisation of type IV collagen and laminin in the tumour tissues was investigated using the indirect immunofluorescence method. Sections were incubated with normal rabbit serum as a control.

Serum concentrations of type IV collagen and laminin were measured with RIA kits for 7S collagen (Hoechst AG, Frankfurt, Germany) and for the P-1 fragment of laminin (Nippon ODC Co, Tokyo, Japan), respectively. Thirty two healthy female volunteers, age range eight to 63 years, served as controls. Serum was obtained from the patient the day before, the day after, and seven days after the operation. All serum samples were tested in duplicate.

Results
Type IV collagen and laminin were expressed strongly in the tumour and seemed to be local-
Figure 1  Granulosa cell tumour stained with (A) haematoxylin and eosin and immunostained for (B) type IV collagen and (C) laminin. Original magnification ×125.

Table 1  Serum concentrations of type IV collagen and laminin before and after removal of the granulosa cell tumour

<table>
<thead>
<tr>
<th>Days after operation</th>
<th>-1</th>
<th>1</th>
<th>7</th>
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<tbody>
<tr>
<td>7S collagen (ng/ml)</td>
<td>18.7</td>
<td>10.6</td>
<td>4.3</td>
</tr>
<tr>
<td>Laminin P-1 (U/ml)</td>
<td>4.9</td>
<td>1.9</td>
<td>0.8</td>
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Discussion

Many granulosa cell tumours are hormonally active and most are oestrogenic. In women of reproductive age, irregular menstrual bleeding or, less often, amenorrhea results from oestrogen production by the tumour. Chronic oestrogen stimulation may lead to atypical hyperplasia, as in the present patient or, in rare cases, to well differentiated endometrial adenocarcinoma.

There have been a few studies on the extracellular matrix of granulosa cell tumours. A recent study has suggested that granulosa cells express type IV collagen mRNA during follicle formation. In our patient, circulating concentrations of type IV collagen and laminin were very high and declined rapidly after surgical removal of the tumour. In addition, strong immunostaining for both type IV collagen and laminin was observed in the tumour, and these basement membrane components were localised to the pericellular region of the granulosa cells. The tumour also showed massive necrotic change and degeneration. These findings suggest that the increased serum concentrations of type IV collagen and laminin might have resulted from either increased synthesis or degradation of these components in the tumour.

Serum concentrations of type IV collagen and laminin are high in patients with liver fibrosis of different aetiologies—for example, those with chronic hepatitis, liver cirrhosis, and alcoholic liver disease, various malignant tumours, and during pregnancy.

Increased deposition of basement membrane components, such as type IV collagen and laminin, in the perisinusoidal walls has been reported in patients with liver fibrosis. Additionally, Brocks et al have reported that in their study serum laminin concentrations were increased in about 50% of patients with cancer. This increase may be explained by destruction of the basement membrane as a result of tumour invasion and increased synthesis of the fibroelastic components surrounding the tumour.

Serum laminin concentrations are also raised throughout pregnancy and decrease rapidly after delivery. Production of basement membrane by the placenta might be the cause of these increased serum concentrations.

In patients with granulosa cell tumour, serial measurement of the serum concentrations of basement membrane components, such as type IV collagen and laminin, in conjunction with other tumour markers and oestrogen concentrations, might be helpful in evaluating prognosis of ovarian granulosa cell tumours, in detecting metastatic or recurrent lesions and in monitoring response to treatment.
Inflammatory pseudotumour and Rosai-Dorfman disease of soft tissue: a histological continuum?

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Abstract
A lesion of the chest wall in a 34 year old woman, which had a combination of histological and immunophenotypic features of inflammatory pseudotumour and Rosai-Dorfman disease of soft tissue, is described. There was considerable overlap in the pathogenesis, histology and immunophenotype of these two lesions. The similarities between these two lesions suggest that there is a temporal sequence and a histological continuum with early histiococyte-rich and late fibroblast- and myofibroblast-rich lesions. Alternatively, the morphological and immunophenotypic features could be because of aberrant cytokine expression in an inflammatory pseudotumour, resulting in transformation of histiocytes to resemble those seen in Rosai-Dorfman disease.

Keywords: inflammatory pseudotumour; Rosai-Dorfman disease; histiocytosis.

Sinus histiocytosis with massive lymphadenopathy (SHML or Rosai-Dorfman disease (RDD)) was first described as a distinct clinicopathological entity that presents with striking lymph node enlargement, often affecting the cervical lymph nodes. It has subsequently been reported in extranodal sites (skin, soft tissues, bone, and nasal mucosa) in up to 43% of reported cases. Histologically, this condition is characterised by a proliferation of large pale cells which show striking lymphohistophagocytosis and immunoreactivity for S100 protein. The histogenesis of the proliferating cell is uncertain but it has features of both Langerhans cells and phagocytes.

Inflammatory pseudotumour is the preferred term for a tumour-like mass of inflammatory origin, which has been reported in various organs and sites. Several other terms, such as plasma cell granuloma, xanthomatous pseudotumour, fibrous xanthoma, inflammatory myofibrohistiocytic proliferation and inflammatory myofibroblastic tumour, have also been used to describe this lesion. The aetiology and nosology of this lesion remain uncertain. The majority of inflammatory pseudotumours are idiopathic. The lesion is usually excised because the clinical and radiological appearances often suggest malignancy.

We report an unusual soft tissue lesion in a 34 year old Asian woman which showed a combination of features of inflammatory pseudotumour and Rosai-Dorfman disease of soft tissue. We suggest that these two lesions are part of a spectrum of inflammatory or reactive conditions, or both, occurring in soft tissues.

Case report
A 34 year old woman presented with a 2 cm superficial, firm, mass on the chest wall of short duration. There were no enlarged lymph nodes. She had had a splenectomy 15 years earlier. The reason for the splenectomy was unknown. Laboratory investigations revealed a normocytic normochromic anaemia. There were no other significant findings on history, physical examination and blood investigations. The mass was excised with a wide margin.

The patient is well without any evidence of recurrence or lymphadenopathy six months after resection.

Methods
The tissue was fixed in formalin and processed for histological examination. Immunohistochimical studies were done on formalin fixed,