Background

Acute Exacerbation (AE) is a lethal factor in patients with usual interstitial pneumonia (UIP). Some reports have suggested clinical features that predict AE such as body mass index (BMI), modified Medical Research Council scale, forced vital capacity (FVC), and Krebs von den Lungen-6 (KL-6). However, pathologic indicators that predict AE are still unknown at present.

If a histologic predictive marker is identifiable by pathologists, pathologists can give a warning of future AE occurrence, then clinicians may change the way of follow-up for their patients. We reviewed cases of UIP to find indicators which could predict AE.

Methods

Histologic candidates for the predictive marker of AE were mostly selected based on the characteristic findings as seen in cases of acute lung injury (ALI) and reported prognostic marker of UIP. The 12 histologic candidates are stated below.

- Organizing pneumonia focus
- Epithelial denudation
- Fibrin
- Kuhn’s hyaline
- Interlobular septal widening
- Edema (air spaces)
- Neutrophilic infiltration
- Edema (interstitium)
- Avascular hemorrhage
- Squamous metaplasia
- Fibroblastic focus

Two observers graded each of the 12 histologic candidates into scores of 0 to 3 and classified them into negative (0) or positive (1, 2, 3). The consensus were obtained afterwards by discussion which also included another pathologist.

Clinical data such as smoking status, BMI, pulmonary function tests, serologic markers of interstitial pneumonia, and patients’ status with follow-up term were also collected.


Association between the classifications of each candidate and AE was investigated using Fisher’s exact test and logistic regression.

Survival analysis was performed by log rank test. Kaplan-Meier curves were also plotted.

Objective

Squamous metaplasia: Indicator of Acute Exacerbation and Poor Prognostic Factor in Usual Interstitial Pneumonia

Masatake Hara, Mikiko Hashisako, Yasuhiro Yamano, Takeshi Johkoh, Yasuhiro Kondoh, Hiroyuki Taniguchi, Junya Fukuoka

Nagasaki University, Nagasaki Educational and Diagnostic Center of Pathology (NEDCP), Tosei General Hospital, Kinki Central Hospital

We found that squamous metaplasia in UIP could predict an acute exacerbation and a poorer prognosis.

References


The limitations are that patient number was small and the study was retrospective. It is necessary to collect more cases and validate data prospectively.

Figure 1. Squamous metaplasia
A) Squamous metaplasia in microscopic honeycombing (circle).
B) Squamous metaplasia (circle) beside a fibroblastic focus (arrow head).
C) Squamous metaplasia covering alveolar septal walls (circle).
D) Classical squamous metaplasia.
E) Squamous metaplasia, H&E (E) and Immunohistochemistry for CK14 and p40 (F).

Figure 2. Cumulative incidence of AE

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>AE (n=20)</th>
<th>Non AE (n=71)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y.o)</td>
<td>61.6 ± 11.2</td>
<td>54.4 ± 7.9</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current or ex-smoker</td>
<td>10 (50%)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>10 (50%)</td>
<td>25 (42%)</td>
</tr>
<tr>
<td>BMI</td>
<td>26.2 ± 3.6</td>
<td>23.9 ± 3.0</td>
</tr>
<tr>
<td>%V/C (%)</td>
<td>73.3 ± 13.9</td>
<td>52.3 ± 21.0</td>
</tr>
<tr>
<td>%FEV1 (%)</td>
<td>84.6 ± 14.1</td>
<td>98.4 ± 20.5</td>
</tr>
<tr>
<td>%FVC (%)</td>
<td>72.6 ± 14.2</td>
<td>91.5 ± 21.5</td>
</tr>
<tr>
<td>%KL (%)</td>
<td>52.1 ± 13.6</td>
<td>74.0 ± 20.3</td>
</tr>
<tr>
<td>PaO2 (kPa)</td>
<td>147 ± 36</td>
<td>84.9 ± 12.5</td>
</tr>
<tr>
<td>LDI (UL/L)</td>
<td>264 ± 53.8</td>
<td>421 ± 157</td>
</tr>
<tr>
<td>KL6 (UL/L)</td>
<td>6191 ± 1286</td>
<td>1326 ± 1229</td>
</tr>
<tr>
<td>SP-D (ng/ml)</td>
<td>375 ± 310</td>
<td>273 ± 219</td>
</tr>
<tr>
<td>Death (n)</td>
<td>15 (75%)</td>
<td>23 (32%)</td>
</tr>
</tbody>
</table>

Table 2. Sensitivity and specificity of squamous metaplasia

<table>
<thead>
<tr>
<th>AE (n=20)</th>
<th>Non AE (n=71)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous metaplasia (+)</td>
<td>18</td>
<td>42</td>
</tr>
<tr>
<td>Squamous metaplasia (-)</td>
<td>2</td>
<td>29</td>
</tr>
</tbody>
</table>

Figure 3. Event (AE) free survival in UIP patients with and without squamous metaplasia

Figure 4. Kaplan Meier overall survival in UIP patients with and without squamous metaplasia

- A median duration until the onset of AE was 497 days (4-2139 days) (Figure 2).
- Histologically, squamous metaplasia showed positive association to the event of AE (RR was 4.65 [1.36, 17.7], p=0.015).
- Fibroblastic focus, known as poor prognostic factor in UIP, did not associate with AE (p=0.34).
- Squamous metaplasia was associated with a worse event free survival in UIP patients (p=0.035) (Figure 3).
- Cases with squamous metaplasia showed significant worse prognosis compared to those without squamous metaplasia (p=0.049) (Figure 4).