胃腸道間質瘤及預後因子之研究

Study of the gastrointestinal stromal tumor and its prognostic factors

中文摘要

胃腸道的軟組織瘤，在過去皆依形態學被分類成平滑肌瘤或肉瘤，而且因爲它的發生率比起腺癌來講是相對很少的，所以對於它的研究就沒有像腺癌那麼多，隨著免疫化學染色及電子顯微鏡的研究，對於大部分的胃腸道軟組織瘤的細胞分化是否是平滑肌細胞便有所質疑；本實驗針對臺北醫學大學過去在胃腸道的 78 個病患共 84 個被診斷爲平滑肌腫瘤或是神經鞘瘤的病例，用免疫化學染色重新探討它們可能的分化，結果顯示 65 個腫瘤是屬於 CD 117 或是 CD 34 陽性但 desmin 陰性的胃腸道間質瘤(gastrointestinal stromal tumor)，其分布以胃部最多，小腸次之；有 13 個腫瘤是 muscle specific actin 及 desmin 皆陽性但 CD117 及 CD34 皆陰性的平滑肌腫瘤，食道、胃、及直腸皆會出現；有 6 個是 S-100 表現很強但 CD117、CD34、muscle specific actin 及 desmin 皆陰性的神經鞘瘤， 4 例是在胃部，2 例在小腸，這個結果說明大部分的胃腸道軟組織腫瘤都不是平滑肌腫瘤；而利用此染色的結果去分析這些在光學顯微鏡下極相似的三種腫瘤，發現在型態上也有細微的變化可以初步分辨出此三種不同的腫瘤，那就是在神經鞘瘤都可以見到腫瘤周圍的很多的淋巴球浸潤，而平滑肌細胞瘤則常表現出三種腫瘤中最低的細胞密度(cellularity)，不過最終仍需經由免疫化學染色方法的確定，本實驗結論之一是對於此類胃腸道的軟組織瘤至少必須染五種不同的抗體來做正確的診斷，那就是 CD117、CD 34、desmin、依 muscle specific actin 以及 S-100。

在胃腸道軟組織瘤中，用免疫染色方法將其進一步分類是有其臨床之重要意義，因爲根據文獻及本研究之病例，正確診斷的神經鞘瘤，幾無惡性的病例出現；而診斷成平滑肌腫瘤的也少有惡性之病例，本研究中這兩類腫瘤有長期追蹤之病患皆有良好的預後，未見有惡性的變化出現；反之大多數的惡性軟組織腫瘤幾乎皆是胃腸道間質瘤。

本研究也用其他胃腸道外之軟組織瘤如平滑肌瘤及肉瘤和神經鞘瘤作爲對照，結果發現這些腫瘤也不會表現 CD117 及 CD34，顯示胃腸道間質瘤是一種與平滑肌腫瘤及神經鞘瘤不同的腫瘤，而胃腸道中之細胞中唯一會同時表現 CD 117 及 CD 34 的是 Cajal 氏間質細胞，所以胃腸道間質瘤可能跟 Cajal 氏間質細胞有關。

預後的因子的研究發現在病理上良性、惡性度不確定的間質瘤間與惡性間質瘤的 MIB-1 指數是有統計上明顯的差異(兩者 $p<0.001$)，惡性間質瘤會有較高的 MIB-1 指數 但進一步運用在病理上的診斷仍需更多病患追蹤的資料作爲佐證。惡性的間質瘤中會發生轉移的及不會發生轉移的，MIB-1 指數也有明顯差異

(p=0.032)，所以惡性腫瘤中，MIB-1 指數高則腫瘤容易有轉移或復發的惡性行爲。
良性、惡性不確定 與惡性間質瘤在 CD44s 及 bcl-2 之表現有差異 (CD44s:p<0.001, bcl-2:p=0.042) ，在惡性的腫瘤中 CD44s 及 bcl-2 的表現就會減少，也可以作爲診斷惡性之參考。

英文摘要

The majority of soft tissue tumors of gastrointestinal tract were diagnosed as leiomyomas or leiomyosarcomas because they morphologically resembled the smooth muscle tumors in other organs. Their incidence was relatively rare, compared with that of adenocarcinomas of the gastrointestinal tract. The studies of soft tissue tumors of gastrointestinal tract were also relatively rare. Due to the immunohistochemical and ultrastrucural investigations, smooth muscle cell origin in most soft tissue tumors of gastrointestinal tract was doubted.
In this study, 78 patients with 84 gastrointestinal soft tissue tumors from the department of pathology of the Taipei Medical University Hospital were included. These tumors were previously diagnosed as smooth muscle tumors or neurilemmomas. By immunohistochemical study, sixty-five tumors were reclassified as gastrointestinal stromal tumors (GISTs), with expression of CD117 and/or CD34. Desmin was not expressed in these tumors. The most common site of GISTs was stomach. The second most common site was small intestine. Another thirteen tumors were reclassifed as leiomyomas, with expression of muscle specifc actin and desmin. But they were negative for CD117 and CD34. They were distributed in the esophagus, stomach, and rectum. The other six tumors were neurilemmomas, with strong S-100 expression. But they were negative for CD117, CD34, muscle specific actin, and desmin. They were located in the stomach and small intestine.
Some morphological differences existed between the neurilemmomas, leiomyomas, and gastrointestinal stromal tumors. The neurilemmomas showed prominent lymphoid cuffing, not seen in the leiomyomas and gastrointestinal stromal tumors. The lowest cellularity was found in the leiomyomas. But the definite diagnosis depended on the immunohistochemical study.
At least five antibodies-CD117, CD34, muscle specific actin, desmin, and S-100 were needed for definite diagnosis of the gastrointestinal soft tissue tumors. The correct diagnosis could provide some prognostic meanings. According to the English literatures, nerve sheath tumors and smooth muscle tumors had excellent prognosis. No malignancy was reported in the nerve sheath nerve tumors. The incidence of leiomyosarcoma was also rare. In the study, the patients with

leiomyomas and neurilemmomas in the gastrointestinal tract also had good prognosis after adequate follow up.

In this study, uterine smooth muscle tumors and soft tissue nerve sheath tumors showed no expression of CD117 and CD34. The only cell in the gastrointestinal tract which could co-express CD117 and CD34 was interstitial cell of Cajal. The interstital cells of Cajal may be the origin of the gastrointestinal stromal tumors.

The significant difference between the MIB-1 index of pathologically benign GIST and that of pathologically malignant GIST was found ($p<0.001$). The significant difference between the MIB-1 index of GIST with uncertain malignant potential and that of pathologically malignant gastrointestinal stromal tumors was also noted ($p<0.001$). The pathologically malignant GIST tended to have higher MIB-1 index. There was different MIB-1 index ($p=0.032$) between the malignant GISTs with adverse event (metastasis, recurrence, and dead of disease) and the malignant GISTs without adverse event. The former had higher MIB-1 index. More clinical follow up data was needed before application of the result on daily pathological diagnosis.

The expression of CD44s and bcl-2 in benign GISTs, GISTs with uncertain malignant potential, and malignant GISTs was significantly different (CD44s: $p<0.001$, bcl-2: $p=0.042$). The expression of CD44s and/or bcl-2 could be probably used for the distinction between benign and malignant GISTs.