The cause of digital clubbing is unknown. Hepatocyte growth factor (HGF) is a pleiotrophic factor which has various biological effects. We measured serum HGF in 12 patients with digital clubbing; the underlying diseases of these patients were: lung cancer, 2; cystic fibrosis, 2; idiopathic pulmonary fibrosis, 3; lung cancer with idiopathic pulmonary fibrosis, 1; chronic hepatitis, 1; interstitial pneumonia with collagen disease, 2; and bronchiectasis, 1; nine hundred and fifty-seven normal volunteers and 17 lung cancer patients without clubbing served as the control. As a result, the serum HGF concentration in patients with digital clubbing (0.47±0.29 ng/ml) was significantly higher when compared to that of lung cancer patients without digital clubbing (0.15±0.04, p<0.01). Therefore, we suggest that HGF may play a role in the formation of digital clubbing.

Key words: idiopathic pulmonary fibrosis, lung cancer

Introduction

Dickinson and Martin have suggested that digital clubbing might be caused by the release of platelet-derived growth factor (PDGF) from impacted megakaryocytes and platelets in the capillaries of the digital nail beds (1, 2). In addition, Fox et al supported this hypothesis by the pathological evidence that numerous platelet microthrombi are evident in patients’ nail beds at autopsy (3). Hepatocyte growth factor (HGF), which is also released from platelets (4), is a pleiotrophic factor which has various biological effects on different cells. In vivo, HGF might be involved in tissue regeneration, tumor progression, and embryological processes (5). In addition, it has been suggested that HGF plays an important role in the process of limb formation. Recently, we treated a patient with an acute exacerbation of chronic hepatitis in whom digital clubbing had rapidly worsened within a month.

Case Report

Case report and measurement of serum HGF in patients with digital clubbing

A 48-year-old man with liver failure progressing to cirrhosis by hepatitis B viral infection had finger clubbing. In this patient, who was afflicted with an acute exacerbation of chronic phase (GOT 1,012 U//, GPT 744 U//, T-Bil 5.3 mg/dl, heparplasin test 20%), the clubbing worsened in accordance with liver failure, and extraordinarily high HGF (30.1 ng/ml). After we treated the patient with antithrombin III, his liver function and clubbing improved, and HGF was reduced (1.21 ng/ml).

Based on this background, we hypothesized that HGF may also play an important role in the formation of digital clubbing. Therefore, we measured serum HGF in 12 patients with digital clubbing (6 males/6 females, median age 56). The diagnosis of digital clubbing was based on the most practical and objective criterion that clubbing is present when the distal phalangeal depth of the index finger is the same or greater than the interphalangeal depth (measured between the second and third phalanges of the index finger). The underlying diseases of these patients were lung cancer, 2; cystic fibrosis (2, identical twins who had a Japanese mother and a German father), idiopathic pulmonary fibrosis, 3; lung cancer with idiopathic pulmonary fibrosis, 1; chronic hepatitis, 1; interstitial pneumonia with collagen disease, 2; and bronchiectasis, 1. HGF was measured by enzyme-linked immunosorbent assay with monoclonal and polyclonal antibodies against human HGF (Otsuka Assay Laboratories, Tokushima). Nine hundred and fifty-seven normal volunteers and 17 lung cancer patients without clubbing served as the control. As a result, the mean (SD) serum HGF concentration of the patients with digital clubbing was 0.47 (0.29) ng/ml, which was significantly higher compared to normal volunteers [0.20 (0.07) ng/ml, p<0.01] and lung cancer patients.
HGF and Digital Clubbing

1.2

Present case

Cystic fibrosis

Bronchiectasis

IPF

Cystic fibrosis

IPF

IPF

Lung cancer

Lung cancer + IPF

Collagen lung (2)

Without clubbing

Clubbing

(n=17)

(n=12)

(0.15±0.04)

(0.47±0.29)

Hepatocyte growth factor (ng/ml)

Lung cancer

without digital clubbing [0.15 (0.04) ng/ml, p<0.01] (Fig. 1).

Discussion

Digital clubbing has been associated with a variety of neoplastic, pulmonary, cardiovascular, and gastrointestinal disorders. However, the mechanism of clubbing remains unknown. Vasodilator and humoral theories have been proposed to account for clubbing (6, 7). Other investigators have suggested that local platelet activation with subsequent release of PDGF plays an important role in digital clubbing. As PDGF is known to stimulate proliferation of mesenchymal cells, and is chemotactic for fibroblasts as well as smooth muscle cells, PDGF was thought to be the most important humoral cytokine in the pathogenesis of digital clubbing. However, there is no direct evidence that proves the relationship of PDGF and digital clubbing.

HGF, which is also released from platelets and mesenchymal cells, controls the proliferation and morphogenesis of epithelial cells. HGF was first detected in the plasma of partially hepatectomized rats as a potent mitogen for adult rat hepatocytes in primary culture and was purified to homogeneity from rat platelets (4). In vivo, HGF is proposed to be involved in tissue regeneration, tumor progression, and embryological processes (5). In addition, it has been suggested that HGF plays an important role in the process of limb formation.

In the lung, HGF is synthesized and secreted by mesenchymal cells, such as macrophages, endothelial cells, and fibroblasts, and controls proliferation and morphogenesis of epithelial cells (8). It has recently been revealed that the lung has an endocrine function and produces HGF for the regeneration of injured tissues or organs (9). HGF also acts as a “pulmotrophic factor” on lung regeneration after acute lung injury (10) and is a potential paracrine growth factor for rat alveolar type II cells in primary culture (8). Furthermore, HGF concentrations in sera of patients with various lung diseases are significantly higher compared to those in healthy donors (10). We also showed previously that serum HGF concentration in patients with pneumonia was significantly higher compared to patients without pneumonia, and the increase of serum HGF followed shortly after the onset of inflammation (11). This suggests that HGF has an important role in the regeneration of the lung following acute lung injury, and HGF could be an indicator of lung repair after lung damage in patients with lung disease (11). Maeda et al have also suggested that serum HGF levels are increased in inflammatory lung diseases including interstitial pneumonitis, and the HGF levels in the surviving patients rapidly decrease with treatment (12).

In the present study, serum HGF concentration in patients with digital clubbing was significantly higher compared to normal volunteers and patients with lung cancer without digital clubbing. Digital clubbing is frequently observed in patients with chronic liver failure, chronic respiratory infection, and idiopathic pulmonary fibrosis, and the concentration of serum HGF in these patient groups were reported to be high (11, 12). In contrast, in 2 patients who have digital clubbing as well as lung cancer, the HGF concentration in sera was not so high. As we experienced only 2 such cases, it was difficult to explain this evidence. However, it was possible to speculate that antigenically different molecules might be secreted from lung cancer. Although the exact role of HGF in the pathogenesis of digital clubbing should be elucidated by an animal experiment, HGF might be an interesting candidate as a humoral factor responsible for digital clubbing. Further clinical study will be needed to confirm the relationship between HGF and digital clubbing.

References

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