厚生労働科学研究費補助金（難治性疾患政策研究事業）
分担研究報告書

重症酒さ、鼻瘤の遺伝的研究

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研究要旨

酒皶は、赤ら顔を基礎とする疾患群で、紅斑毛細血管拡張型、丘疹膿疱型、腫瘤・鼻瘤型の3型に分類される。日本では皮膚科医を除いて、一般人と一般医療関係者での認知度の低い疾患である。日本人には少ないと考えられているが、不快な火照り感を感じる人々は多く、認知度が低いために日本人ではその頻度が実情よりも低く考えられている。とくに最重症型とされる鼻瘤・腫瘤型酒皶では、鼻部を中心とした顔面正中部に進行性の変形を伴うため、患者のQOLの低下が著しく、社会生活上で問題となることも多い。

酒皶の病態は不明であるが、最近の研究で外界刺激を関知する自然免疫系の異常・過敏性が指摘されるようになってきた。これらの自然免疫系の過敏性や酒皶は白人や人種差に影響される側面も見いだされ、何らかの人種差や遺伝学的背景をもって発症していることが想定されている。しかしながら、詳細な遺伝学的検討の報告は漸く為されつつあり状況であり、詳細は全くの不明である。また日本人における発症頻度も不詳であり、日本人における背景を検証する必要がある。

酒皶患者の疫学調査、遺伝背景検索をおこなうために精緻かつ均一な酒皶患者の診断をおこなうことは、必要な手続きである。そこで、平成26年度には酒皶の診断基準を策定することに主眼を置き、診断基準と重症度判定基準を策定した。これら酒皶診断基準に基づき、平成27年度には、酒皶の疫学調査のために、全国の主要基幹施設にアンケート調査を行った。

共同研究者
なし

A．研究目的

発症要因が不明である酒皶の病態解明に取り組むことを本研究の目的とする。白人に多いなどの遺伝的背景を示唆する臨床観察・知見に基づき、日本人での酒皶の疫学、遺伝的背景を調査することを目的とした。

B．研究方法

平成26年度に策定した酒皶の診断基準、重症度判定基準、除外診断をもとに、全国の主要基幹施設にアンケート調査を行った。主たる対象疾患は腫瘤・鼻瘤型の酒皶とした。酒皶特に腫瘤・鼻瘤型酒皶の頻度を検討するために、腫瘤・鼻瘤型酒皶患者が比較的集積されると想定される大学病院を主体としてアンケートを送付した。質問項目は、過去三年間で酒皶、鼻瘤、酒皶様皮膚炎（ステロイド皮膚炎）と診断された患者数である。医師へのアンケートを主体とした研究であるので、倫理面への配慮は特にない。

C．研究結果

全国で113施設の大学病院皮膚科宛にアンケートを送付し、62施設から回答を得た（回収率54.9%）。過去三年間に酒皶、鼻瘤、酒皶様皮膚炎と診断

された患者数は、それぞれ 1881 名、81 名、878 名であった。一施設あたりの酒皶、鼻瘤、酒皶様皮膚炎の平均患者数は、それぞれ 30.4 名、1.3 名、14.2 名であった。実数の報告では、酒皶は愛知県、東京都、神奈川県、大阪府、栃木県、宮城県の順に報告が多く、鼻瘤では大阪府、福岡県、宮城県、埼玉県で 8 名以上の報告が為された。人口 100 万人あたりに換算すると、酒皶では奈良県の 77.4 名が最も多く、次いで栃木県と愛知県に 50 名以上の患者数と試算された。人口 100 万人あたりの酒皶、鼻瘤、酒皶様皮膚炎患者頻度はそれぞれ平均で 18.6 名、0.7 名、8.7 名と試算された。

D．考察

今回の調査では、大学病院皮膚科を主たる調査対象とし、62 施設から回答を得た。酒皶や酒皶様皮膚炎の様な比較的よく起こる疾患は、大学病院に紹介されることは多くないと想定されるため、今回の調査での酒皶や酒皶様皮膚炎の実数は低く算定されていると考える。鼻変形を伴う重症の鼻瘤患者は、基幹病院を紹介されることが多いと推定されるが、レーザーや美容形成術の施術を受ける場合には、大学病院皮膚科以外を受診しているであろう。これらを鑑みると、今回の調査の数倍以上の患者が潜在していると推察される。

E．結論

平成 26 年度に策定した酒皶の診断基準、重症度判定基準、除外診断を元に、大学病院皮膚科を主体とした疫学調査を行った。酒皶の遺伝的背景の検索では、全世界的に見てもまだ、ゲノム関連解析や、転写領域シークエンス解析、全ゲノムシークエンス解析などの系統だった解析が行われていない。将来には、日本人での症例の集積から遺伝的背景の解析が必要と考える。

F．健康危険情報

なし

G．研究発表

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H．知的所有権の出願・登録状況
（予定を含む）

1．特許取得
なし

2．実用新案登録
なし

3.その他
なし

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[IV]
研究成果の刊行に関する一覧表

1.雑誌

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研究成果の刊行物・別刷

Epiplakin Is a Paraneoplastic Pemphigus Autoantigen and Related to Bronchiolitis Obliterans in Japanese Patients

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All plakin family proteins are known to be autoantigens in paraneoplastic pemphigus (PNP). In this study, we first examined whether PNP sera also react with epiplakin, another plakin protein, by various immunological methods using 48 Japanese PNP sera. Immunofluorescence confirmed that cultured keratinocytes expressed epiplakin. Epiplakin was detected by 72.9% of PNP sera by immunoprecipitation-immunoblotting with KU-8 cell extract, but not by immunoblotting of either normal human epidermal extract or KU-8 cell extract. Epiplakin was essentially not detected by 95 disease and normal control sera. Statistical analyses of various clinical and immunological findings revealed a significant correlation of the presence of anti-epiplakin antibodies with both bronchiolitis obliterans and mortality. No epiplakin-negative PNP case developed bronchiolitis obliterans. However, although 29.4% of European patients with PNP had bronchiolitis obliterans, significant correlation with anti-epiplakin autoantibodies was not observed. In further studies for lung, immunofluorescence showed the presence of epiplakin in normal human lung, particularly respiratory bronchiole, immunoprecipitation-immunoblotting showed that PNP sera reacted with epiplakin in cultured lung cells, and mice injected with polyclonal antibody specific to epiplakin histopathologically showed abnormal changes in small airway epithelia. These results indicated that epiplakin is one of the major PNP autoantigens and is related to PNP-related bronchiolitis obliterans.

Journal of Investigative Dermatology (2016) **136,** 399–408; doi:10.1038/JID.2015.408

INTRODUCTION

Paraneoplastic pemphigus (PNP), or paraneoplastic autoimmune multiorgan syndrome (Nguyen et al., 2001), is an autoimmune blistering skin disease with severe mucocutaneous lesions. PNP is commonly associated with hematological malignancies (Anhalt, 1997; Anhalt et al., 1990). Histopathology shows acantholysis and apoptotic cells in epidermis and interface changes (Anhalt, 1997; Anhalt et al., 1990; Billet et al., 2006; Sehgal et al., 2009).

Prognosis of PNP is poor with approximately 68% mortality (Leger et al., 2012). Particularly, all PNP cases with chronic respiratory disease show fatal outcome (Nousari et al., 1999; Takahashi et al., 2000). Severe inflammation occurring in respiratory bronchioles leads to irreversible fibrotic reaction, resembling bronchiolitis obliterans (BO). In a previous study, BO occurred in 6% of 53 European patients with PNP (Leger et al., 2012), whereas the prevalence was 25% in our recent study for 107 Japanese patients with PNP. However, pathogenesis in PNP-related BO is currently unknown.

PNP develops autoantibodies to various antigens, mainly plakin family proteins. Immunoprecipitation (IP) first detected the 250-kDa desmoplakin I, the 230-kDa bullous pemphigoid 230 (BP230), the 210-kDa doublet of desmoplakin II and unknown protein, and the 190-kDa and 170-kDa unknown proteins (Anhalt et al., 1990). Then, immunoblotting (IB) of normal human epidermal extract showed that all PNP sera reacted with the 210-kDa and 190-kDa doublet proteins (Borradori et al., 1998; Hashimoto, 2001; Hashimoto et al., 1995). Thereafter, the 210-kDa and 190-kDa proteins were identified as envoplakin (EPL) and periplakin (PPL), respectively (Kiyokawa et al., 1998). This reactivity is very useful for

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Abbreviations: BO, bronchiolitis obliterans; BP, bullous pemphigoid; Dsg, desmoglein; EPL, envoplakin; EPPK, epiplakin; IB, immunoblotting; IF, immunofluorescence; IHC, immunohistochemistry; IP, immunoprecipitation; NHSAE, normal human small airway epithelial; pAb, polyclonal antibody; PNP, paraneoplastic pemphigus; PPL, periplakin; RP, recombinant protein

Received 25 June 2014; revised 23 September 2015; accepted 26 September 2015; accepted manuscript published online 19 October 2015

diagnosis of PNP (Joly et al., 2000; Mouquet et al., 2008; Poot et al., 2013). Plectin, another plakin protein, was also found to be PNP autoantigen (Proby et al., 1999). Thus, all known plakin proteins are PNP autoantigens.

Non-plakin proteins are also detected by PNP sera. ELISAs detected antibodies to desmoglein 3 (Dsg3) and/or Dsg1 in PNP sera (Amagai et al., 1998; Brandt et al., 2012). We also found that the unknown 170-kDa protein was alpha-2-macroglobulin-like-1 (Numata et al., 2013; Schepens et al., 2010), and BP180 was frequently reacted by PNP sera (Tsuchisaka et al., 2014).

Epiplakin (EPPK) was originally identified as an autoantigen in a patient (Fujiwara et al., 1996), and is expressed in entire epidermis, skin appendices, and other intestinal epithelia (Fujiwara et al., 2001). Subsequent studies showed that EPPK is a plakin protein with many repeats of plakin-specific B-domain and linker-domain (Spazierer et al., 2003; Takeo et al., 2003). EPPK connects intermediate filaments (Spazierer et al., 2006, 2008; Wang et al., 2006). Despite abundant expression of EPPK in stratified and simple epithelia, gene-targeted mice showed no abnormality in either phenotype or keratin filament organization, except for mild delay of wound healing (Goto et al., 2006, Ishikawa et al., 2010).

Because EPPK is a plakin protein, we speculated that EPPK might also be a PNP autoantigen. In this study, we investigated whether anti-EPPK antibodies were present in PNP sera by various analyses. Immunoprecipitation-immunoblotting (IP-IB) detected anti-EPPK autoantibodies in 35 of 48 PNP sera. Statistical analysis indicated correlations of anti-EPPK antibodies with PNP-related BO and mortality. Additional studies indicated that EPPK is expressed in respiratory cells and tissues and was reacted by PNP sera, suggesting that anti-EPPK autoantibodies may develop BO.

RESULTS

Clinical and immunological parameters for all 48 Japanese patients with PNP are summarized in Supplementary Table S1 online.

Immunohistochemistry (IHC) and immunofluorescence (IF) of normal human skin, KU-8 cells, and rat bladder

By IHC and IF of normal human skin, rabbit polyclonal antibody (pAb) for human EPPK (anti-EPPK pAb) (Figure 1a and c), but not normal rabbit IgG (Figure 1b and d), showed cytoplasmic staining in entire epidermis. By IF, anti-EPPK pAb (Figure 1e), but not normal rabbit IgG (Figure 1f), showed perinuclear cytoplasmic staining in cultured KU-8 cells. Finally, by IF using the rat bladder, anti-EPPK pAb (Figure 1g), but not normal rabbit IgG (Figure 1h), showed cell surface and cytoplasmic reactivity.

IB of normal human epidermal extract

We first attempted to detect anti-EPPK antibodies in 48 Japanese PNP sera by IB of normal human epidermal extract. Anti-EPPK pAb detected approximately 500-kDa EPPK (Supplementary Figure S1 online). However, whereas all PNP sera detected the 210-kDa EPL and 190-kDa PPL, neither PNP nor normal sera reacted with EPPK.

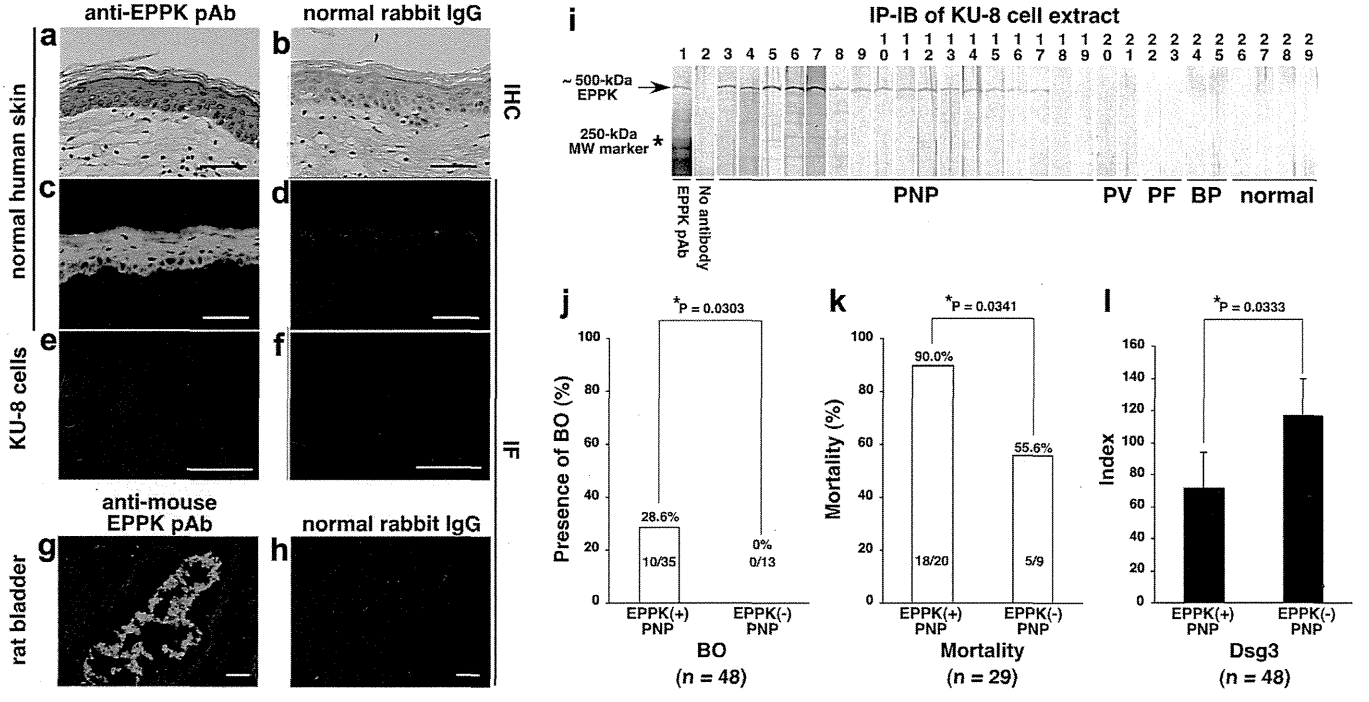

Figure 1. EPPK detection in normal human skin and KU-8 cells. (**a, b**) IHC of normal human skin with anti-EPPK pAb and normal rabbit IgG. (**c–h**) IF of normal human skin (**c, d**), KU-8 cells (**e, f**), and rat bladder (**g, h**). Bars = 50 μm. (**i**) IP-IB of KU-8 cell extract for EPPK with anti-EPPK pAb (lane 1), no antibody (lane 2), PNP (lanes 3–19), PV (lanes 20, 21), PF (lanes 22, 23), BP (lanes 24, 25), and normal sera (lanes 26–29). The positions of the approximately 500-kDa EPPK and the 250-kDa molecular marker are shown on the left. (**j–l**) Statistical analyses for association of BO (**j**), mortality (**k**), and ELISA indices for Dsg3 (**l**). Asterisks (*) indicate statistically significant differences between EPPK(+) PNP and EPPK(−) PNP ($P < 0.05$). BO, bronchiolitis obliterans; BP, bullous pemphigoid; Dsg, desmoglein; EPPK, epiplakin; IF, immunofluorescence; IHC, immunohistochemistry; IP-IB immunoprecipitation-immunoblotting; pAb, polyclonal antibody; PNP, paraneoplastic pemphigus; PV, pemphigus vulgaris.