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H、知的財産権の出願、登録状況

特になし

厚生労働科学研究費補助金（難治性疾患克服研究事業）
好酸球性食道炎／好酸球性胃腸炎の疾患概念確立と治療指針作成のための臨床研究
分担研究報告書

特殊な形態を呈した好酸球性胃腸炎に対する治療

研究分担者　松本主之　九州大学病院消化管内科　講師

研究要旨

特殊な形態を呈した好酸性胃炎に対してステロイドとロイコトリエン拮抗薬による治療を試みた。患者は64歳の男性である。強い心窩部痛を主訴に来院、胃体部を中心に多発潰瘍を認めた。末梢血の好酸球と血清IgEの増加に加え、生検で好酸球の浸潤を認めたため好酸球性胃腸炎と診断した。プレドニゾロンの投与で好酸球数、血清IgEともに低下し症状も消失、潰瘍も瘢痕化した。同薬の減量に加えてロイコトリエン拮抗薬の併用投与を行ったが再発を来したため、プレドニゾロンを増量して治療を継続している。現在はハイドロキシウレアやシクロスポリンを中心とした免疫調整薬の併用投与を検討中である。

研究協力者

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はじめに

好酸球性消化管疾患（eosinophilic gastrointestinal disorders; EGID）は、消化管への著明な好酸球浸潤と多彩な消化器症状がみられる比較的まれな疾患であり、好酸球浸潤を認める部位により好酸球性食道炎、好酸球性胃腸炎、好酸球性大腸炎に分類される。本邦では好酸球性胃腸炎の頻度が高いとされるが、その画像所見は多彩である。今回我々は、多発潰瘍を呈した好酸球性胃腸炎を経験したので、その臨床経過を検討した。

症例

患　者：60歳代、男性。

主　訴：心窩部痛。

既往歴：小学生時に虫垂炎で虫垂切除術を施行されている。気管支喘息や食物アレルギーの既往なし。

家族歴・生活歴：特記事項なし。

現病歴：40歳頃に心窩部痛が出現し、その後上部消化管内視鏡検査で反復して胃潰瘍を指摘され、その度H. pylori陰性と診断されていた。2010年12月上旬に強い心窩部痛を自覚したため近医で上部消化管内視鏡検査を受け、胃に大小の多発潰瘍を指摘された。プロトンポンプ阻害薬の投与で症状が軽快したため2011年2月にH2受容体拮抗薬へ変更されたところ、同年3月の内視鏡検査で潰瘍性病変が増大したため入院となった。

入院時現症：心窩部痛に圧痛を認めるほか、異常なし。

検査成績：白血球数は9860/μLで好酸球数は1090/μL（11.1%）と軽度増加し、CRPは0.93mg/dlと軽度上昇していた。血清IgEは13836g/dlと著明高値を示し、蛍光酵素免疫測定法によるアレルギーテストでは小麦、卵白、コメ、卵黄、エビ、カニに対して陽性反応がみられた。血清のHP-IgG抗体は陰性であった。上部消化管内視鏡検査では胃体上部後壁に巨大な開放性潰瘍を認め、その辺縁は粘膜下腫瘍様に隆起していた。その他にも穹隆部大弯、体上部前壁、体中部大弯に小潰瘍が多発していた（図1）。食道、十二指腸、小腸および大腸には異常を認めなかった。また、腹部CTでは胃体部の壁肥厚を認めるのみであった。消化管各所より生検を施行したところ、胃からの生検組織において好酸球の集簇を認めた（図2）。慢性好酸球性白血病の可能性を考え、骨髄穿刺を施行したが、骨髄像および染色体分析で異常は指摘出来なかった。以上よ

り、胃に限局し多発潰瘍を呈した好酸球性胃腸炎と診断した。

経過：プレドニゾロン 40mg/ 日を開始したところ心窩部痛は速やかに消失した。上部消化管内視鏡検査で潰瘍の縮小傾向がみられたためプレドニゾロンを漸減した。潰瘍の瘢痕化を確認し、プレドニゾロンを 2mg/ 日まで減量しロイコトリエン拮抗薬の併用を開始した。しかし、プレドニゾロンを 1mg/ 日まで減量した時点で心窩部痛が出現し、上部消化管内視鏡検査でも潰瘍の再発が確認された。プレドニゾロンを再度 40mg/ 日まで増量したところ症状は消失したため減量をしつつある。ハイドロキシウレアやシクロスポリンなどの免疫調整薬の経口投与を現在検討中である。

考察

好酸球性胃腸炎は、発症頻度が 10 万人あたりの発症数が 1 から 20 と比較的まれな疾患で、20 ～ 50 歳代の男性に好発する。欧米では Talley ら[1] の診断基準が広く用いられているが、本研究班から本邦好酸球性胃腸炎の実態に基づいて作成した診断指針（案）[2] も提唱されている。自験例はいずれの診断基準も満たしていた。

本症は好酸球の主な浸潤部位と臨床症状により、predominant mucosal layer disease、predominant muscle layer disease、predominant subserosal layer disease の 3 病型に分類されている[3]。自験例は多発潰瘍を形成していたこと、心窩部痛が主症状であったこと、腸管狭窄はなく腹水貯留も明らかでなかったことから、predominant mucosal layer disease とするのが妥当と考えられた。しかし、上記病型が混在する症例も少なからず存在することから、西村ら[4] はそれらを transmural disease として別個に取り扱うべきであると述べている。

臨床的には、本症に特異的な症状や画像所見はなく、上記病型、すなわち好酸球浸潤の部位、程度、範囲などで臨床像は異なっている。Predominant mucosal layer disease では粘膜の発赤や肥厚、びらんなどが中心となり、胃内でも幽門前庭部に好発する。自験例のように体部に潰瘍を形成した症例の報告も散見されるが、多発潰瘍を呈する症例はまれである。

好酸球性胃腸炎に対する治療法の中心は、対症療法、および副腎皮質ステロイドや抗アレルギー薬の投与である。一方、高度の腸管狭窄を有する症例や消化管穿孔を来した症例では外科的切除が選択肢となる。しかしながら、これらの治療に一旦は反応するものの、再発を繰り返す症例が少なくない。自験例においても、一旦はステロイドに良好に反応したが、減量とともに再発し、その後の治療法に難渋している。

好酸球増多と消化管への好酸球浸潤を特徴とする疾患群として、好酸球増多症候群（hypereosinophilic syndrome; HES）がある。HES は、寄生虫感染やアレルギー性疾患などの基礎疾患がなく、末梢血に 1500/μL 以上の高度な好酸球増加が 6 ヶ月以上持続して認められ、臓器障害を伴う疾患群の総称である[5]。その一部は好酸球性胃腸炎と重複するが、HES ではハイドレアやインターフェロン、シクロスポリン、イマチニブなどの有効性が報告されている[6-9]。自験例は HES の診断基準は満たさないものの、今後の難治性の経過が予想され、HES に準じた治療を考慮すべきであろう。ただし、これまでに好酸球性胃腸炎に対するシクロスポリンの効果に言及したのは、一昨年の本研究班報告書のみである[2]。

自験例は、比較的特異な多発潰瘍の形態を呈した好酸球性胃腸炎であり、難治性・再発性の臨床経過が観察できた点でも貴重と思われた。EGID に顕著な胃粘膜病変を主たる臨床像とするものが存在することに留意し、今後同様の症例を集積すべきと考えられる。

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健康危険情報

なし

研究発表

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知的財産権の出願・登録状況

特許取得：特になし

実用新案登録：特になし

その他：特になし

図1：胃内視鏡所見。胃体上部後壁に巨大な潰瘍を形成している。体中部大弯にも小潰瘍が多発している。

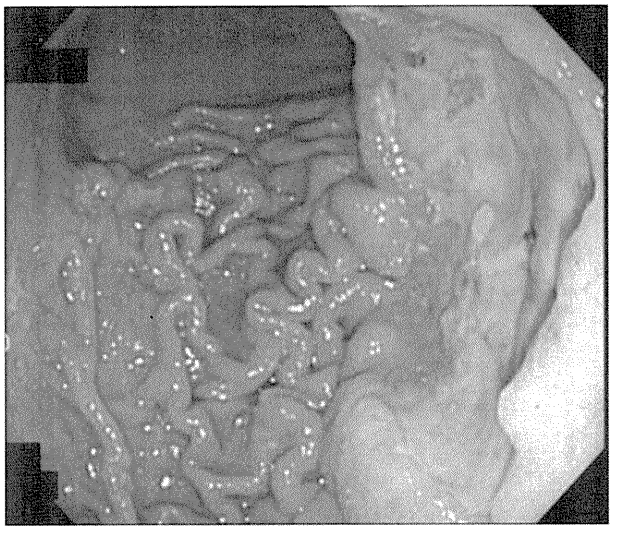
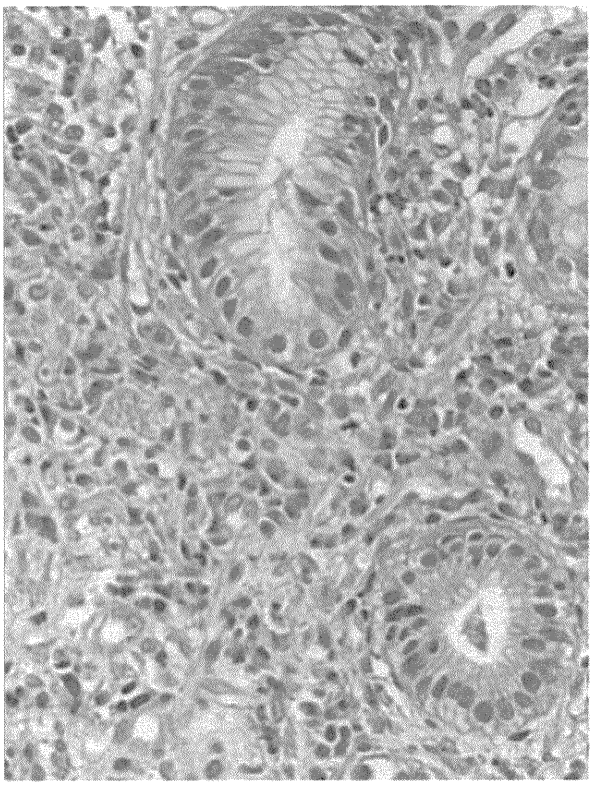


図2：胃生検病理組織所見。胃粘膜内に好酸球の浸潤あり。



厚生労働科学研究費補助金（難治性疾患克服研究事業）
好酸球性食道炎 / 好酸球性胃腸炎の疾患概念確立と治療指針作成のための臨床研究
分担研究報告書

食道への好酸球性侵潤が食道運動機能に及ぼす影響に関する研究

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研究要旨

食道への好酸球性侵潤の食道運動機能に及ぼす影響は明らかではない。今回、食道に好酸球侵潤を有する症例に対する治療前後の検討から、食道への好酸球侵潤が下部食道括約筋（LES）弛緩不全および食道体部の運動異常の原因となっている症例が存在することが判明した。

研究協力者

岩切勝彦（日本医科大学消化器内科・准教授）

A. 研究目的

好酸球性食道炎患者の主な症状は嚥下困難である。内視鏡所見では狭窄を有することもあるが、その頻度は39.7%（1）であり、嚥下困難の原因として食道運動機能異常の存在は考えられる。好酸球性食道炎患者の食道機能を検討した報告では全体の40.1%に異常を認める報告（1）され、運動異常としてはLES弛緩不全、体部運動異常が報告されている。今回、食道に好酸球侵潤を有する好酸球性食道炎患者および食道・胃・十二指腸に好酸球侵潤を認めた好酸球性胃腸症患者の治療前後の食道運動機能をhigh resolution manometry（HRM）により評価し、食道への好酸球性侵潤が食道運動機能に及ぼす影響を明らかにする。

B. 研究方法

対象は「つかえ感」を主訴に来院し精査の結果、食道に20個以上/HPFの好酸球侵潤を認めた好酸球性食道炎（71歳､女性）および食道･胃･十二指腸に20個以上の好酸球侵潤を認めた好酸球性胃腸炎（73歳、男性）の2例である。

治療前の食道内圧検査および、好酸球性食道炎、好酸球性胃腸症に対する治療後、自覚症状、血液検査所見が改善した約1か月後に内視鏡を行い食道の生検を行い好酸球侵潤がほぼ消失したことを確認後、治療後の食道内圧検査を施行し食道への好酸球侵潤の影響を検討した。

食道内圧検査は6時間以上の絶食後、鼻孔より4mmの内圧カテーテルを挿入後、先端3か所の圧センサーが胃内圧を少なくとも3か所測定できる部位にカテーテルを設置した。5分間の安静後、下部食道括約筋（LES）静止圧を5分間測定し、その後、水5mlの嚥下によるLES弛緩および食道体部運動の評価を20-30秒間隔にて10回行った。

C. 研究結果

<u>症例1（71歳の女性。好酸球性食道炎症例）</u>

「つかえ感」を主訴に来院。食道にのみ好酸球侵潤を認め好酸球性食道炎と診断した。食道内圧検査での水嚥下の結果は、10回ともほぼ同様であり、30mmHg未満の弱い収縮波の蠕動を何とか確認できるが、30mmHg以上の収縮波を有効収縮波とした場合には、蠕動波は下部食道においてのみ観察された。LES圧も低値（10mmHg未満）であった。治療は食事摂取も困難な状況であったため、PSL30mgの経口投与を行った。PSL内服後の翌日より症状改善し、3日目には症状は完全に消失した。血液データにおいても末梢の好酸球数（治療開始前の好酸球性数は1279/μℓ）は翌日より減少、2日目には正常化した。その後、PSLの減量を行ったが、症状、好酸球数の再燃は認めなかった。4週後に内視鏡検査を再施行した所、治療前に観察された通常観察、ヨード散布後の多数の輪状溝は観察されず、また治療前には十分に観察されなかった

粘膜の血管透見も観察されるようになった。中部～下部食道にかけて3個の生検を行ったが好酸球は確認できなかった。その後の食道内圧検査では、水嚥下後の収縮波の評価では、蠕動波の収縮圧は治療前より圧の上昇がみられ、蠕動があることは治療前に比べ容易に確認できるが有効収縮波である30mmHg以上の収縮波の評価では明らかな違いは認めなかった。

症例2（73歳の男性。好酸球性胃腸炎：好酸球浸潤—> 食道、胃、十二指腸）

内視鏡検査では中部食道より肛側では狭小化しており、収縮もあり送気しても十分に伸展しない状況であった。また深吸気時にも食道胃接合部の伸展は得られず、柵状血管は観察されず、アカラシア患者において観察される下部食道の全周性の襞集中像（Esophageal Rosette）が観察された。狭小部の生検より好酸球20個以上/HPFが確認された。胃、十二指腸にも散在する発赤を認め、同部位の生検より好酸球20個以上/HPFが確認された。胸部CT検査においても中部食道から下部食道における全周性の壁肥厚を認めた。

食道内圧検査では、ほとんどの嚥下に伴い中部食道から下部食道において100mmHg以上の強い同期性収縮が観察され、この強収縮波が存在する部位は内視鏡での狭小部位と一致していた。また、嚥下後のLES弛緩不全がみられ、LES圧は高値であり、100mmHgを超える時間帯もあった。内圧所見からはvigorous achalasiaの所見であった。

治療は食事摂取も困難な状況であったため、PSL30mgの経口投与を行った。PSL投与後の翌日より症状改善を認め、3日目に完全消失となった。血液検査においても末梢の好酸球数は投与前約3800/μℓから3日目には正常化した。その後、PSL漸減を行うが症状の再燃は認めなかった。約4週後の内視鏡検査では、中部食道にやや狭小化している部分が観察されたが、治療前と比べ明らかな改善が認められた。中部食道から肛側の血管透見もみられた。下部食道では深吸気時に柵状血管の下端を含めた、ほぼ全体像が観察されるようになった。中部から下部食道の生検においても好酸球は認めなかった。

治療後約1カ月の食道内圧検査では嚥下後のLES弛緩不全は認めず、食道上部においては蠕動波の出現不良であったが平滑筋領域では蠕動波を認め、ほぼ正常な食道運動であった。

D. 考察

過去の好酸球性食道炎患者における食道運動異常の有無を検討したレビューでは全体の40.1%に食道運動異常（LES弛緩不全が18.4%、体部運動異常28.6%、【重複あり】）が認められたと報告（1）されている。これらの運動異常が原因であるのか、結果であるかは明らかでないが、好酸球性食道炎の主な症状が「つかえ感」であることを考えると、食道運動異常、特にLES弛緩不全が「つかえ感」の原因となっている症例も存在すると考えられる。

食道への好酸球浸潤を有する症例に対する治療前後の検討から、食道への好酸球浸潤がLES弛緩不全および食道体部の運動異常の原因となる症例が存在することが明らかとなった。特に症例2においては好酸球浸潤によりLES弛緩不全、蠕動異常を呈し、アカラシア症状を認めた症例である。アカラシアの発症はLES弛緩、一次蠕動波に関連する中枢、外来迷走神経、食道壁内神経叢のどこか、または複数個所の異常により発症すると考えられているが、原因は未だ明らかではなく、アカラシア発症を考える上で大変興味ある症例である。症例2においてはPSLによる治療が遅れた場合には、LES弛緩不全が不可逆的であった可能性も否定できない。

E. 結論

食道への好酸球浸潤が食道運動異常を引き起こすことがある。日常診療において、原因が明らかでない「つかえ感」症例の診療において、食道への好酸球浸潤による食道運動異常が原因である可能性も念頭に置き診療する必要がある。

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H. 知的財産権の出願・登録状況

1. 特許取得
   特になし
2. 実用新案登録
   特になし
3. その他
   特になし

Ⅲ. 研究成果の刊行に関する

一覧表

研究成果の刊行に関する一覧

雑　誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Ⅳ. 研究成果の刊行物・別刷

Review

Digestion

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Roles of Milk Fat Globule-Epidermal Growth Factor 8 in Intestinal Inflammation

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Key Words
MFG-E8 · Intestinal inflammation · Apoptosis · $\alpha_v\beta_3$-Integrin · Phosphatidylserine

Abstract
Milk fat globule-epidermal growth factor 8 (MFG-E8), a glycoprotein secreted from various cells, enhances engulfment of apoptotic cells by forming a link between phosphatidylserine on apoptotic cells and $\alpha_v\beta_3$-integrin on phagocytes. This process is essential for maintaining the host immune system under physiological conditions. Apart from this scavenging function, MFG-E8 also directly regulates a variety of cellular functions, such as attenuating inflammation and healing of injured tissues. Furthermore, recent studies have revealed that MFG-E8 has anti-inflammatory and regenerating roles during intestinal inflammation. This review highlights novel findings regarding the roles of MFG-E8 in intestinal pathophysiology as well as its therapeutic potential for gut inflammatory disorders. Copyright © 2012 S. Karger AG, Basel

Introduction

Apoptotic cells are rapidly engulfed by phagocytes to avoid the release of numerous inflammatory mediators from dying cells. This function is essential for maintaining immune homeostasis and highly regulated by various unique molecular mechanisms. The glycoprotein milk fat globule-epidermal growth factor 8 (MFG-E8) was originally discovered as a mammalian milk fat globule membrane component. Later, it was shown that MFG-E8 binds to apoptotic cells and bridges them to phagocytes for accelerating engulfment [1]. Severe inflammatory and autoimmune consequences with abnormal homeostasis in MFG-E8 null mice are due to infiltration by apoptotic cells [2]. Recent studies have also revealed that MFG-E8 is functionally involved in the pathogenesis of sepsis, ischemia, atherosclerosis, and neurodegenerative disorders [3–6].

In addition to its scavenging function, MFG-E8 was shown to be effective in attenuating inflammation, by controlling epithelial integrity and healing of injured mucosa in the intestinal tract [7, 8]. Those functions have been suggested to be dependent not only on enhanced clearance of apoptotic cells, but also on various novel molecular mechanisms. We recently reported that MFG-E8 attenuated in-

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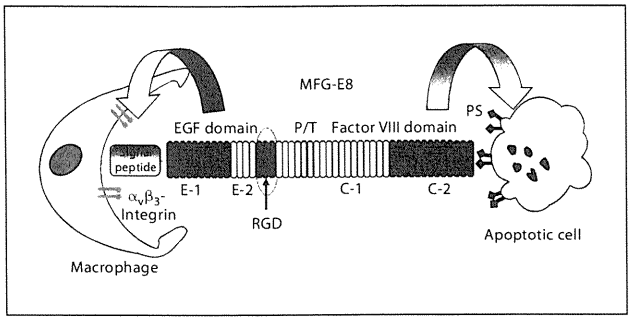

Fig. 1. Structure and noble functions of MFG-E8. The long form of murine MFG-E8 is a 64-kDa glycoprotein, with two cysteine-rich EGF domains at the N-terminus and two discoidin-like domains resembling blood coagulation factor V/V111 at the C-terminal site. The nascent MFG-E8 peptide possesses a signal sequence that directs the protein to be secreted into the extracellular region. The most prominent function of MFG-E8 is to clear apoptotic cells by forming a link between PS on apoptotic cells and $\alpha_v\beta_3$-integrin on phagocytes.

testinal inflammation in murine experimental colitis by modulating $\alpha_v\beta_3$-integrin signaling [9]. Since the intestinal tract is one of the major immune organs that contributes to maintaining normal tissue homeostasis, as well as regulating infections and inflammation, it is reasonable to speculate that MFG-E8 plays important roles in preserving intestinal functions. The aim of the present review is to highlight recent findings regarding the role of MFG-E8 in intestinal pathophysiology as well as its therapeutic potential for treatment of intestinal inflammation.

Features of MFG-E8: Expression Profile and Its Regulation

The MFG-E8 gene is located on chromosome 7 in mice and chromosome 15 in humans. In mouse tissues, MFG-E8 is expressed as two different isoforms, termed short and long forms [1]. The structure of long-form MFG-E8 is shown in figure 1. MFG-E8 possesses two epidermal growth factor (EGF) repeats at the N-terminal and the blood coagulation factor V/VIII at the C-terminal end, while an arginine-glycine-aspartate (RGD) motif is contained in the second EGF repeat. MFG-E8 participates in phagocytosis of apoptotic cells by forming a link between phosphatidylserine (PS) on apoptotic cells and $\alpha_v\beta_3$-integrin on phagocytes [1].

MFG-E8 expression was initially discovered in samples obtained from lactating mammary glands. However, recent reports revealed that MFG-E8 is also ubiquitously expressed in the brain, heart, lungs, intestines, liver, and kidneys under normal physiological conditions [10–12]. We examined MFG-E8 expression in different tissues of normal BALB/c mice and observed high levels in the colon, spleen, lungs, and kidneys [9]. In each organ, MFG-E8 is expressed in a variety of cell types, including mammary epithelial cells, macrophages, splenocytes, dendritic cells, fibroblasts, vascular smooth muscle cells, glail cells, and astrocytes [13–18].

In various tissues and cells, MFG-E8 expression is tightly regulated by several factors and stimuli. Prolactin (PRL), a growth hormone, as well as insulin and steroid hormones are potent stimulators of MFG-E8 expression in their target cells [11, 19, 20]. We recently investigated the effects of PRL on MFG-E8 expression in macrophages by evaluating its promoter function [21]. Following treatment with PRL, significant up-regulation of MFG-E8 was observed in macrophages, while its effect was mediated by the presence of a responsive element of the transcription factor C/EBPβ in the MFG-E8 promoter. In addition, hormone-related regulation of MFG-E8 production, fractalkine (a CX3C chemokine), peroxisome proliferator-activated receptor (PPAR)-δ ligand, and granulocyte macrophage colony-stimulating factor (GM-CSF) have also been reported to induce MFG-E8 expression [16, 22, 23]. These factors are up-regulated in sites of inflammation in organs, suggesting that MFG-E8 may play essential roles for attenuating inflammation and regenerating injured tissues.

In contrast to the above findings, LPS is known to down-regulate MFG-E8 expression in macrophages. Komura et al. [3] used LPS-induced septic mice and found that endotoxemia decreased the endogenous levels of MFG-E8 in serum and several organs. Their findings also indicated that LPS-induced down-regulation of MFG-E8 expression in macrophages is mediated via the Toll-like receptor 4 (TLR4)/CD14 pathways.

MFG-E8 Expression in Intestinal Tissues with Normal and Pathophysiological Stress

As in other tissues and organs, basal levels of MFG-E8 expression have been observed in different compartments of mice gut tissues, e.g. the stomach, and small and large intestines, while that expression level in the colon was shown to be relatively higher as compared to the stomach and small intestine [9]. Furthermore, an immunohistochemical study detected MFG-E8 expression in lamina propria mononuclear cells in mice colonic sections.

On the other hand, altered MFG-E8 expression has been found during intestinal inflammation. We recently examined changes of MFG-E8 expression during dextran sulfate sodium (DSS)-induced colitis in mice [9]. In that model, MFG-E8 expression was dramatically reduced during the acute phase of the disease, while it gradually became elevated during the regeneration phase after DSS in water intake was stopped and finally returned to a normal level when the disease was abrogated. Similar time-course changes of MFG-E8 expression were also found in a trinitrobenzene sulfonic acid (TNBS)-induced colitis model [24]. In an experimental model of sepsis established by cecal ligation and puncture, MFG-E8 levels in small intestinal tissues were markedly decreased [7]. Moreover, severe injury and inflammation were induced in small intestines of mice after intestinal ischemia and reperfusion (I/R), which decreased MFG-E8 levels in the spleen and other affected tissues [25]. Thus, MFG-E8 expression is down-regulated during the acute and severe inflammatory phases of intestinal disorders.

Although the underlying mechanism of this decreased production of MFG-E8 has not been clearly revealed, the abundance of pro-inflammatory mediators and involvement of LPS/TLR4 signaling may play important roles. One recent speculation states that the increased expression of MFG-E8 in injured intestinal mucosa during the acute phase of DSS-induced colitis may be due to the extent of inflammation and/or variations in mouse strains [26]. Consistent with these findings, in the majority of stress-induced disease conditions, e.g. renal I/R, alcohol-intoxicated septic animals, and human atherosclerosis plaques, MFG-E8 expression has been found to be abruptly decreased [4, 8, 27].

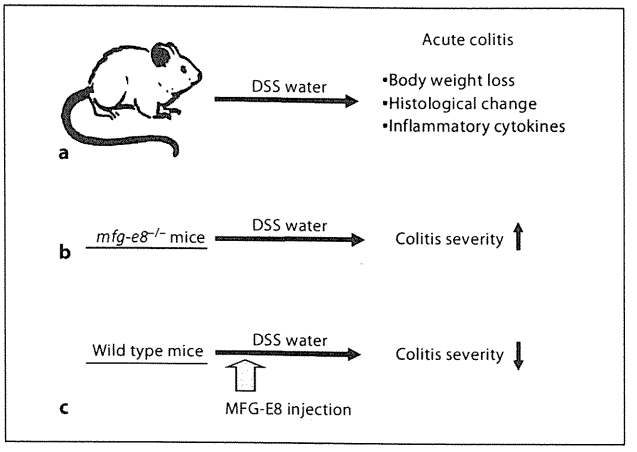

Fig. 2. Anti-inflammatory effects of MFG-E8 on DSS colitis. **a** Mice given DSS in drinking water showed clinical, histological, and inflammatory signs of colitis. **b** DSS-induced colonic inflammation in MFG-E8 null mice was more severe than that in wild-type mice. **c** rMFG-E8 effectively ameliorated the development of DSS-induced colitis by attenuating inflammation and disease status.

Roles of MFG-E8 in Intestinal Inflammation

Anti-Inflammatory Effects

Based on our findings of down-regulation of MFG-E8 during DSS-induced colitis, we treated mice with recombinant MFG-E8 (rMFG) and observed its beneficial effect to inhibit intestinal inflammation (fig. 2) [9]. In addition, an anti-inflammatory effect of rMFG was shown in a mouse model of I/R-induced intestinal injuries [25]. A recent study also revealed that DSS-induced colonic inflammation in MFG-E8 null mice is more severe than that in wild-type mice [26], indicating that MFG-E8 plays a crucial role in inhibiting intestinal inflammation (fig 2). In injured intestinal mucosa of MFG-E8 null mice, infiltration of apoptotic cells was not clearly evident, suggesting that the protective role of MFG-E8 is not only due to efficient clearance of apoptotic cells, but also that this glycoprotein directly modulates innate immune functions [7]. Mice treated with rMFG-E8 at the onset of acute colitis showed significant down-regulation of the tissue contents of pro-inflammatory cytokines from inhibition of NF-κB activation [9]. During activation of the innate immune system, integrin signaling pathways are up-regulated, which then recognize potent ligands to boost the intracellular inflammatory cascade. Osteopontin (OPN) is an extracellular matrix phosphoprotein that contains the RGD domain, which is predominantly expressed in macrophages and induces the production of NF-κB-mediated inflammatory cytokines after binding to $\alpha_v\beta_3$-integrin. We employed several in vitro experiments and observed that MFG-E8 reduced LPS-induced NF-κB activation by blocking OPN binding, while it also modulated $\alpha_v\beta_3$-integrin-dependent downstream signaling (fig. 3). After OPN binding, activation of $\alpha_v\beta_3$-integrin also results in recruitment of phosphorylated focal adhesion kinase (FAK), leading to NF-κB activation. Moreover, stimulation with LPS increases phosphorylation of FAK to enhance binding of exogenous OPN to $\alpha_v\beta_3$-integrin. By targeting this pathway, MFG-E8 can reduce LPS-induced NF-κB activation by blocking OPN binding, as well as modulation of $\alpha_v\beta_3$-integrin-dependent and FAK-mediated downstream sig-

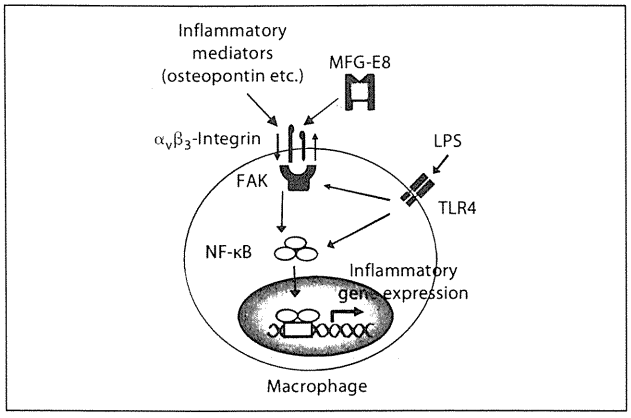

Fig. 3. Anti-inflammatory mediation roles of MFG-E8. LPS activates an innate immune response in macrophages via TLR4 signaling, which augments NF-κB-mediated production of pro-inflammatory cytokines. LPS also up-regulates $\alpha_v\beta_3$-integrin and generates inside-out signaling to promote the binding of several inflammatory mediators, e.g. OPN, which activates $\alpha_v\beta_3$-integrin-mediated outside-in signaling to further augment the downstream pathways. After OPN binding, activation of $\alpha_v\beta_3$-integrin also results in recruitment of phosphorylated FAK, leading to NF-κB activation. Moreover, stimulation with LPS increases phosphorylation of FAK to enhance binding of exogenous OPN to $\alpha_v\beta_3$-integrin. By targeting this pathway, MFG-E8 can reduce LPS-induced NF-κB activation by blocking OPN binding, as well as modulation of $\alpha_v\beta_3$-integrin-dependent and FAK-mediated downstream signaling.

naling (fig. 3). Similar to OPN, high-mobility group protein B1 (HMGB1) has the ability to directly bind to cell surface $\alpha_v\beta_3$-integrin and induce tissue injury during colitis [28, 29]. MFG-E8 also competitively inhibits HMGB1 binding to $\alpha_v\beta_3$-integrin and may ameliorate HMGB1-mediated intestinal tissue injury.

Expressions of $\alpha_v\beta_3$-integrins have been detected in intestinal epithelial cells (IECs) [24]. Also, MFG-E8 can inhibit TLR ligand-mediated production of pro-inflammatory cytokines by modulating NF-κB activation in cultured IECs. This result is quite similar to that observed in an experiment that utilized macrophages. However, the detailed mechanisms of the anti-inflammatory effects of MFG-E8 on IECs remain unknown.

Regeneration Role in Intestinal Injured Tissues

Bu et al. [7] reported that MFG-E8 plays a crucial role in tissue regeneration during the healing process of injured colonic mucosa. They investigated whether MFG-E8 stimulates IEC migration in an in vitro wound-healing model and observed that treatment with rMFG-E8 promoted the migration of IECs by activating intracellular protein kinase C (PKC). In addition, administration of rMFG-E8 to experimental septic mice accelerated mucosal healing by binding to the transiently exposed PS receptor of the injured IECs. In DSS- and TNBS-mediated mice colitis models, increased levels of colonic MFG-E8 were detected during the regenerating phase of colitis [9, 24], which may contribute to healing of injured colonic mucosa by promoting IEC migration. On the other hand, angiogenesis is also a crucial event for intestinal tissue regeneration. MFG-E8 binds to $\alpha_v\beta_3$-integrin on endothelial cells and accelerates vascular endothelial growth factor-induced angiogenesis under physiological and pathological conditions [30], which may contribute to colonic tissue regeneration during inflammation.

Future Perspective

The crucial roles of MFG-E8 have been delineated in several animal models as well as knock-out mice studies that mimicked human intestinal disorders. Notably, MFG-E8 has been shown to have both anti-inflammatory and regenerating roles during colitis. However, most of those findings were obtained in experiments that used acute and severe intestinal inflammation models, and the precise roles of MFG-E8 in chronic gut immune disorders remain largely unknown. Moreover, there have been no studies of the expression and functions of MFG-E8 in human intestinal mucosa. On the other hand, recent findings have revealed direct roles of MFG-E8 in innate immune functions by activating regulatory T cells, and subsequent production of IL-10 and transforming growth factor-β, which may further promote immunoregulatory functions within the tissue microenvironment [31, 32]. Collectively, these results will provide direction for future investigations of MFG-E8 administration for ameliorating gut inflammatory disorders, including inflammatory bowel diseases.

Conclusion

In this review, findings regarding the various roles of MFG-E8 in intestinal tissues are presented, indicating the glycoprotein to be an essential factor for maintaining intestinal homeostasis.

Disclosure Statement

The authors declare that no financial or other conflicts of interest exist in relation to the content of the article.

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CASE REPORT

A case of eosinophilic esophagitis with atypical clinical course

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Abstract Eosinophilic esophagitis is a rare chronic disease that mainly occurs in middle-aged males. Treatment with a glucocorticoid and/or proton pump inhibitor is usually necessary to relieve unpleasant symptoms. An 83-year-old female patient with dysphagia and heartburn was diagnosed with eosinophilic esophagitis based on endoscopic findings, while histological examination identified dense infiltration of intraepithelial eosinophils. The symptoms and eosinophil infiltration spontaneously disappeared without any treatment approximately 2 months later. No obvious lifestyle or dietary changes to explain elimination of possible antigens were identified in this case. We report an atypical case of eosinophilic esophagitis with spontaneous regression.

Keywords Eosinophilic esophagitis · Endoscopy · Glucocorticoid · Dysphagia

Introduction

Eosinophilic esophagitis is a disease characterized by chronic esophageal mucosal inflammation with dense infiltration of eosinophils in esophageal squamous epithelium [1]. It is considered to be caused by local allergic reactions to food or airborne antigens, and affected patients have reported various esophageal symptoms, including food impaction, dysphagia, and heartburn [2]. For diagnosis of eosinophilic esophagitis, characteristic endoscopic findings and identification of dense eosinophilic infiltration in endoscopic biopsy specimens are considered to be important. Eosinophilic esophagitis is reported to be a chronic disease, with a risk of esophageal stenosis caused by long-standing inflammation-induced fibrosis in the esophageal submucosal layer [3, 4]. Fewer than 20 cases have been previously reported in Japan, and all of those patients required drug administration for remission induction, based on a MEDLINE search using "eosinophilic esophagitis" and "Japanese" as keywords. Herein, we report a case of eosinophilic esophagitis in an elderly female, whose symptoms and esophageal eosinophilic infiltration spontaneously regressed without treatment.

Case report

An 83-year-old female periodically visited the outpatient clinic of Okuizumo Hospital for postsurgery follow-up examinations. She had been treated in 2002 for pituitary adenoma by surgical resection and was administered hydrocortisone at 10 mg/day for subclinical postsurgery hypopituitarism. She began to report dysphagia and heartburn when eating food in February 2010. The symptoms gradually worsened, and endoscopic examination was performed in September 2010. Although endoscopy failed to show any organic esophageal diseases, including reflux esophagitis and neoplastic diseases, narrow-band imaging (NBI) revealed shallow linear furrows in the mid-esophagus area (Fig. 1a, b). Other endoscopic findings characteristic of eosinophilic esophagitis, such as multiple rings,

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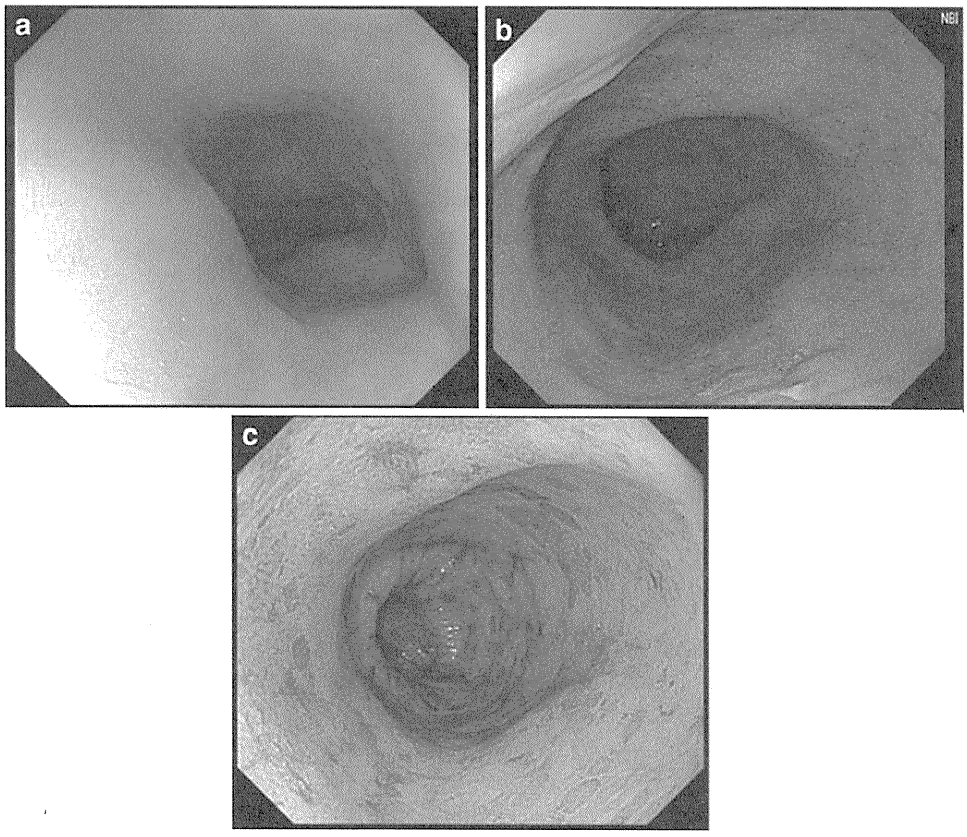

Fig. 1 Endoscopic images obtained with standard white-light (**a**) and narrow-band imaging (**b**). In narrow-band images, longitudinal linear furrows were identified. Lugol staining showed uneven staining of esophageal mucosa (**c**)

white stipple-like exudates, wrinkled pattern, and corrugated esophagus, were not found. Following Lugol staining, brownish change of esophageal mucosa was weak and uneven, suggesting possible diffuse inflammation (Fig. 1c). Two esophageal biopsy specimens taken from the middle and lower esophagus showed dense infiltration of more than 20 eosinophils in a high-power field of esophageal squamous epithelium (Fig. 2). A diagnosis of eosinophilic esophagitis was established, since other clinical conditions related to possible esophageal eosinophilic infiltration were not found.

The patient had no allergic diseases including bronchial asthma and no family history of allergic diseases. Laboratory tests were all within normal ranges, including peripheral blood leukocytes (6750/μl), eosinophils (122/μl), and IgE (22.2 IU/ml). In addition, plasma interleukin (IL)-5, IL-13, IL-15, eotaxin3, and thymic stromal lymphopoietin (TSLP) were all normal. The results of a skin prick test, patch test, and radioallergosorbent test (RAST) for standard allergens were all negative.

Computed tomography (CT) and endoscopic ultrasonography (EUS) showed normal nonthickened esophageal wall. Esophageal high-resolution manometry detected normal esophageal body peristaltic contractions and normal lower esophageal sphincter resting pressure with appropriate relaxation during ingestion (Fig. 3).

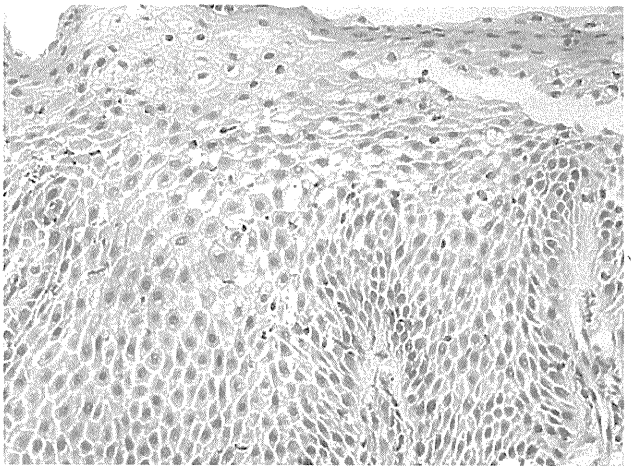

Fig. 2 Photomicrograph of biopsy specimen showing dense infiltration of eosinophilic leukocytes in esophageal squamous epithelium (>20 eosinophils in ×400 high-power field), hematoxylin–eosin staining

Locally active glucocorticoid administration was planned for relieving esophageal symptoms by depressing inflammation caused by eosinophilic infiltration. However, before starting the administration, the symptoms began to gradually decline and nearly disappeared 2 months later. Endoscopic examination performed in November 2010 did not show characteristic findings of eosinophilic esophagitis

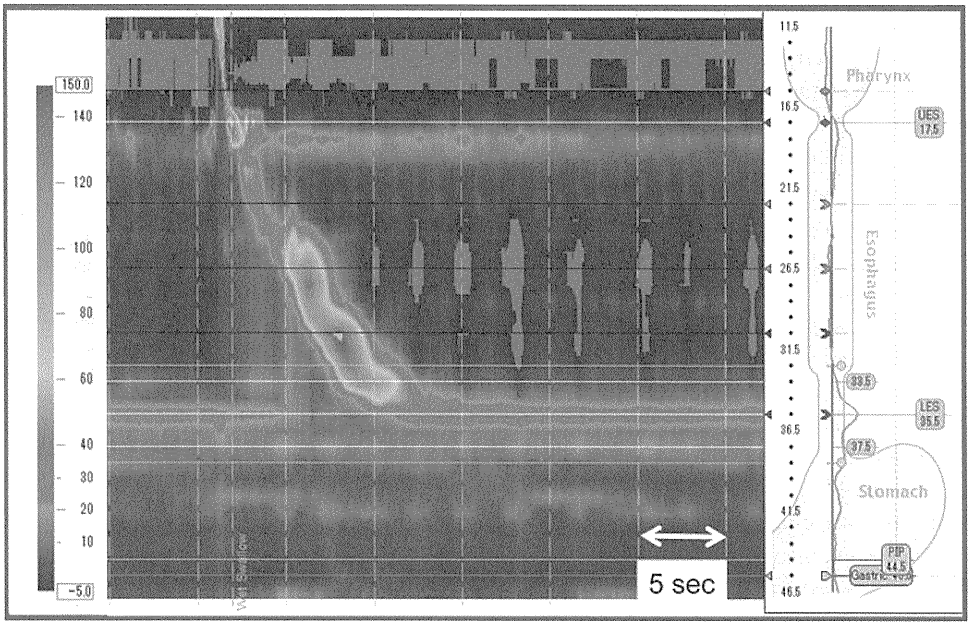

Fig. 3 Esophageal high-resolution manometry findings revealing pressure activity in the esophagus from the pharynx to the stomach. Contractile pressure, peristaltic velocity, and lower esophageal sphincter function were within normal limits. *Reddish color* shows higher levels of pressure

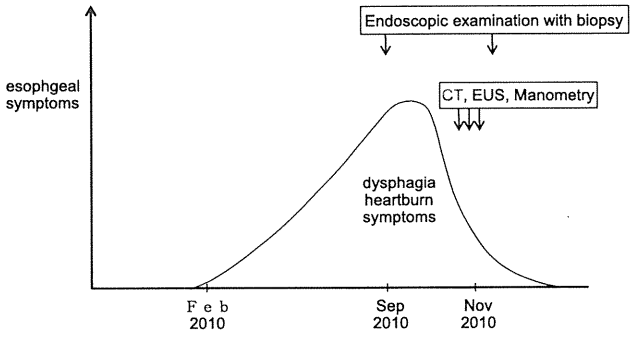

Fig. 4 Illustration of the clinical course. Esophageal symptoms spontaneously disappeared without specific treatment

even with NBI imaging and Lugol staining. Endoscopic biopsy specimens obtained in November 2010 did not show any abnormal infiltration by intraepithelial eosinophils. Thereafter, the patient was regularly examined in the outpatient clinic and confirmed to have no esophageal symptoms without drug administration targeting eosinophilic esophagitis. The clinical course is shown in Fig. 4.

Discussion

Eosinophilic esophagitis is a recurrent long-lasting chronic disease, and cases of spontaneous remission are rare [7]. Straumann et al. [8] reported the rarity of spontaneous remission in adult cases with eosinophilic esophagitis followed for up to 12 years, while Spergeal et al. [9] reported that only 2% of pediatric patients with eosinophilic esophagitis showed spontaneous remission during observation periods as long as 14 years.

Food antigens, especially nuts, soy, wheat, milk, eggs, and seafood, are reported to be related to development of eosinophilic esophagitis, and their elimination from the diet frequently relieves symptoms caused by eosinophilic esophagitis, especially in pediatric patients [10–12]. In animal studies as well as human case studies, airborne allergens such as *Aspergillus* have been reported to be important allergens that cause esophageal infiltration by eosinophils [13–15]. Therefore, elimination of food and/or airborne allergens appropriate for each patient is expected to relieve esophageal eosinophil infiltration with symptom resolution. However, identification of possible allergens in individual patients is difficult, even following skin prick and skin patch tests, or RAST [16], and elimination of a specific food from the diet based on results of those tests has often been reported to be not adequately effective to relieve related symptoms [17].

For treatment of eosinophilic esophagitis, oral glucocorticoid administration is considered to be the standard therapy, with high rates of success reported [1, 18]. To minimize possible adverse effects of glucocorticoid administration, locally active glucocorticoids that are systematically inactive because of rapid catabolism in the liver, such as budesonide and fluticasone, are now used as first-line therapeutic drugs for the disease [19, 20].

Because of wider distribution of information concerning symptomatic and endoscopic characteristics of eosinophilic esophagitis, the number of reports in Japan is increasing [5, 6]. The majority of reported patients are middle-aged males with some allergic complications. In addition, they frequently show ring-like multiple strictures in the esophagus, and require glucocorticoid or proton pump inhibitor administration to control esophageal symptoms.