e. 血清 Th2 ケモカイン TARC（thymus and activation-regulated chemokine, CCL17）

アトピー性皮膚炎の病勢マーカーとして保険収載されている．アトピー性皮膚炎が寛解しているにもかかわらず，TARC が高値を示した場合，消化管の Th2 炎症を示唆していることがある．感度は 30％と低い．

f. 牛乳特異的 IgE 抗体

本質的には IgE は病態との関わりは薄いが，陽性であった場合には，ミルクタンパクを認識する Th2 系細胞の参画があるとの間接証明となる．

g. 皮膚プリックテスト

即時型食物アレルギーの合併有無を確認するときに有用である．

h. 皮膚パッチテスト

有用な場合もまれにあるが，本検査は皮膚ホーミングのアレルゲン特異的 T 細胞があって初めて陽性となりうる．消化管のみに存在するアレルゲン特異的 T 細胞で消化管アレルギーが成立している場合は，陽性とはならない．

i. 腹部単純 X 線撮影

イレウスや壊死性腸炎様の粘膜内ガスの検出に役立つ．

j. 腹部超音波検査

消化管炎症から来る腸管壁肥厚や血流増加を観察することが可能な場合がある．

k. 腹部 CT 検査

主に鑑別目的で行われる．発がん性のデメリットを考慮し，有益性が上回る場合のみ行う．

l. 消化管内視鏡検査，組織検査

体重増加不良や低タンパク血症が存在するクラスター 3 や，血便などの患者で必要となることが多い．また，乳児の炎症性腸疾患，免疫異常に伴う持続消化管炎症などの鑑別に役立つ．熟練した専門医が行う必要があり，体重 3 kg を超えていれば可能である．内視鏡のマクロ所見は，クラスター 3 は異常を認めない場合が多く，顕微鏡観察して初めて診断可能となる．好酸球の著明な増加を見，crypt abscess など他疾患の所見がなければ診断できる．

m. 便粘液好酸球

便の透明ゼリー状に見える粘液部分を採取し，薄くスライドグラス上に塗布，染色して観察する．少数の好酸球は正常新生児でもみられるため，多数であるか，石垣状に集簇がみられた場合にのみ診断できる．

n. 負荷試験における注意点

詳細は別稿（関連ウェブサイト 1），2））に譲るが，注意してほしい点として，2-3 日負荷をして症状が出なかったら，本症ではなかった，もしくは寛解したとするのは自然な考えであろう．しかし，これは間違いである．少なくとも 3 週間連日負荷（chronic tolerance test）して，症状がない場合に初めて，そういえる．

6. 治療と予後

1）必ず症状は寛解する

本症は，食餌治療に成功し，重大な合併症や事象が起きていなければ，必ず症状は寛解する．そして，3 歳頃にはほとんどの児が原因食物を摂取できるようになる．症状が残っている場合は，食餌治療がうまくいっていないか，もしくは診断に見落としがある．

成長曲線をまず書いてほしい．−2 SD 以上なら，健康体重を確保できており，将来への懸念は少ない．−3 SD なら，マイルストーンは遅れていることが多く，1-2 割は不可逆的な障害を残す可能性がある．−4 SD 以下であれば，多くは障害を残す．−2 SD を超える体重を目標としたい．治療方法の詳細は関連ウェブサイト 1），2）をご覧いただきたい．6 大栄養素などに不足が出ないよう，十分な栄養を行うことが何よりも重要である．

2）よくある合併症

消化管閉塞：アレルギー炎症により消化管の浮腫などが起き，閉塞する．

消化管破裂：やはり炎症の結果消化管壁が脆弱となり，穿孔を起こす．

壊死性腸炎：詳細には研究されていないが，壊死性腸炎と同様の壁内ガス像がみられる．腸管壁の血流は保たれていることが多いように思われる．一部は，壊死を起こしており，腸管切

除を必要とする.

貧血：血便がみられる患者に多い.

成長発達の遅れ：栄養障害に起因する. 除去食を行いながら, 6大栄養素や微量元素, ビタミンの不足を起こさないようにする.

いずれも早期発見, 早期治療が鍵となる

3) 予　後

合併症や成長発達障害が起きる前に, 症状を寛解させることができた場合は, 予後は良い. 原因食物の除去が適切になされている場合は, 1歳で50％, 2歳で85％, 3歳で95％が完全に寛解していて, 原因食物を摂取できるようになっている. 原因食物をとり続けている場合, 症状は持続する.

4) 予　防

予防法は確立していない. 新生児-乳児消化管アレルギーにおいては, 次子の妊娠中, 出産後に牛乳や牛由来ミルクの摂取を控えたほうがよいと思い込んでいる保護者もいるが, むしろ摂取して免疫寛容誘導を期待すべきである.

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別冊日本臨牀　新領域別症候群シリーズ　No. 35（2016年1月20日発行）別刷

免疫症候群（第2版）

—その他の免疫疾患を含めて—

II

V. アレルギー性疾患

好酸球増加症候群

好酸球性食道炎—小児と成人を含めて—

木下芳一
沖本英子
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好酸球増加症候群

好酸球性食道炎—小児と成人を含めて—

Eosinophilic esophagitis: pediatric and adult cases

木下芳一
沖本英子
石村典久

Key words：食道炎，好酸球，アレルギー，プロトンポンプ阻害薬，内視鏡検査

1. 概念・定義

消化管にのみ多数の好酸球の浸潤が起こり，それに伴って消化管の傷害と機能障害が起こり消化器症状が出現する病態を好酸球性消化管疾患(eosinophilic gastrointestinal diseases: EGIDs)と総称している．この中で食道粘膜に胃食道逆流症や寄生虫疾患などの好酸球浸潤の原因となる病態がないにもかかわらず病的な好酸球の浸潤が起こり，これが原因となって嚥下障害などの食道症状が出現する病態を好酸球性食道炎と呼んでいる．1980年代に初めてまとまった症例の報告がなされた比較的新しい疾患概念で，病態の解析が最近急速に進んでいる．

本疾患は嚥下障害症状のためにhealth related quality of life(HRQOL)の低下を起こしやすく，また長期炎症が持続すると食道の狭窄を起こし拡張術が必要となりうるため厚生労働省の指定難病の一つに選定されている．

2. 疫　　学

最近急速に患者数の増加がみられ，スイスでは1980年代には有病率が人口10万人あたり2人であったのが2000年代にはその10倍になったことが報告されている．米国の最近の報告では人口10万人あたり50人台の有病率が報告され，発症率も人口10万人あたり年間10人を超えて，アカラシアの10倍の発症率となり，胃食道逆流症についで有病率の高い食道疾患となっている[1]．日本では，一般人口を対象とした本疾患の有病率調査は行われていないが，内視鏡受検例を対象集団とした解析では内視鏡受検例1,000例から5,000例に1人程度の好酸球性食道炎が発見されており，これは同様の欧米での検討と比較すると20-30分の1に当たる[2,3]．本疾患の世界での有病率を見渡すと，気管支喘息などのアレルギー性疾患と類似しており，先進国で高く，開発途上国で低く，日本はその中間である．アフリカでは本疾患の報告例はない．

好発年齢は小児期から中年以降まで広い範囲に及ぶが，欧米の小児を中心とした報告では10歳代が多く，日本での報告では40歳前後が多い[4]．日本では症状が軽度の例が内視鏡診断で発見されることが多く，内視鏡検査を受ける機会の多い成人に高頻度に発見されている可能性があると考えられる．

男女比に関しては欧米の報告でも日本の報告でも男性が多く，全患者の70-80％が男性患者である．

アメリカでの検討では都市部に比べて田舎のほうが有病率が高く，発見されるのは春から夏にかけてが最も多いと報告されている．

3. 病　　因

病因が完全に明らかとなっているわけではないが，食事をアミノ酸成分栄養食にすると多くの例で好酸球浸潤も消失するため食物アレルゲンが病因である可能性が高いと考えられる[5]．

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0047-1852/16/¥60/頁/JCOPY

また，ミルク，小麦，卵，ナッツ，大豆，海産物の6種の食材を除いた除去食で，症状や食道粘膜への好酸球浸潤が改善する例が70％程度はあるため，食物アレルゲンとしてはこれら6種の食品である可能性が高いと考えられている[6]．

ただし，都市部と田舎での有病率の差異や，季節による発症率の差異があることを考えると，環境アレルゲンが関与している可能性も一部にはあると考えられる．

4. 病　　態

一卵性と二卵性の双生児を対象とした検討から好酸球性食道炎の発症に及ぼす遺伝的因子の重みと環境因子の重みが比較され，環境因子のほうが重要で，発症要因の約80％を占めることが報告されている[7]．環境因子としては食物アレルゲンへの感作と再度の食物アレルゲン曝露時の免疫反応が重要で，遺伝的因子としては食物アレルゲンに感作をしたり，感作後再曝露時の炎症の起こりやすさが重要であると考えられる．

遺伝的な要因を検討することを目的としてgenome-wide association study(GWAS)が米国の患者を対象として行われた．その結果，thymic stromal lymphopoietin(TSLP)とcalpain 14(CAPN14)が好酸球性食道炎の発症に関与していることが示唆された[8,9]．TSLPは好酸球性食道炎の食道粘膜で高発現しており免疫系をTh2へシフトさせる作用があることが知られている．一方，CAPN14は食道に特異的に発現しているcalpain familyの分子であり，炎症を抑える作用が注目されている．そこでCAPN14遺伝子に異常があり発現が低下すると食道に炎症が起こりやすい状態となると考えられる．

食道粘膜でどのようなタンパクの産生が増加し，どのようなタンパクの産生が減少しているかが食道粘膜のmRNAをマイクロアレイ解析することで検討された．その結果，filaggrin，involcrinの発現低下，eotaxin 3，IL-5，13，15，periostin，TGFβ，TSLPなどの産生亢進がみられることが明らかとなった[10]．filaggrinとinvolcrinはepidermal differentiation complexといわれる皮膚の扁平上皮の上皮細胞間の接着物質で，産生が低下すると上皮の透過性が亢進すると考えられている．実際にfilaggrinに変異のある例ではアトピー性皮膚炎を発症するリスクが高いことが知られている．eotaxin 3は好酸球の強力なケモカインで食道扁平上皮はIL-4，13の刺激を受けるとeotaxin 3を産生することが示されている．IL-5，13，15はTh2タイプのサイトカインで，IL-5は骨髄での好酸球の産生を促進し，IL-13はeotaxin 3の産生を刺激しeotaxin 3に誘導されて食道粘膜上皮層中に好酸球の浸潤が起こる．periostinやTGFβは線維化を亢進させて食道組織の再構築を起こして食道の狭窄を引き起こすことになる．

これらをまとめて病態を推定すると食物抗原がfilaggrinやinvolcrinの発現が低下した皮膚から浸入し感作を起こす．感作したヒトがその抗原を含む食事をし，抗原が胃酸の食道内逆流で粘膜の透過性が亢進している食道粘膜を介して粘膜下に侵入する．食道粘膜ではTSLPの分泌増加のためにTh2免疫を発動しやすくなっている樹状細胞が抗原刺激を受けTh2反応を誘導する．Th2リンパ球はIL-5を産生して好酸球の骨髄での産生を亢進させ，さらにIL-13を産生して食道扁平上皮を刺激してeotaxin 3を産生させ好酸球を食道粘膜上皮層中に呼び寄せる．食道ではCPAN14の産生が低下しており，炎症が起こりやすい状態となっており，ここに好酸球の脱顆粒で様々な起炎物質が放出されると強い炎症が起こり，periostinやTGFβを介して線維化が起こってくる，と考えられる．

5. 診断と鑑別診断

小児から中年の男性が嚥下障害や食後の胸のつまり感，胸痛，胸やけを訴えたときに好酸球性食道炎の可能性を考えるところから診断が始まる．幼児期には発育障害や逆流症状が，学童期には腹痛や嘔吐が，成人期には嚥下障害が主訴となりやすいとされている．好酸球性食道炎を有する例のうち約半数に何らかのアレルギー性疾患が認められ，最も高頻度に合併するアレ

表1 好酸球性食道炎の診断指針案

1. 症状(嚥下障害，つかえ感等)を有する．
2. 食道粘膜の生検で上皮内に20/HPF以上の好酸球が存在している．
(生検は食道内の数カ所を行うことが望ましい)
3. 内視鏡検査で食道内に白斑，縦走溝，気管様狭窄を認める．
4. CTスキャンまたは超音波内視鏡検査で食道壁の肥厚を認める．
5. 末梢血中に好酸球増多を認める．
6. 男性
7. プロトンポンプ阻害薬は無効でグルココルチコイド製剤が有効である．

1と2は必須．これら以外の他の項目も満たせば可能性が高くなる．

ルギー性疾患は気管支喘息で20-30％の例が気管支喘息の既往歴か現病歴を有している[1]．一方ヘリコバクター・ピロリ感染陽性者は少ない[11]．このためアレルギー歴のある，ヘリコバクター・ピロリ感染陰性例であれば好酸球性食道炎の可能性が高くなる．

血液検査を行って好酸球の増加を同定できる例は好酸球性食道炎では30％程度であるため末梢血中に好酸球増多を認めないことのほうが多い．IgEは70％程度の例で高値を示すが特異性が低く，特異抗原に反応するIgEが高値であるというわけではないので末梢血検査は診断にはあまり有用ではない[12,13]．

上部消化管の内視鏡検査を行うと特徴的な変化がみられる．最も診断に有用性が高いのは縦走溝といわれる縦走し少し発赤し陥凹した数本の溝である[3]．縦走溝は逆流性食道炎の粘膜病変とは違って食道下部以外にもみられ，また溝の幅は逆流性食道炎のmucosal breakよりも狭いため鑑別は可能である．これについで食道の輪状の収縮輪や輪状狭窄，食道粘膜の好酸球のmicroabscessが本態であると考えられている白斑の存在である．さらに特異性は低いが食道粘膜の発赤や浮腫のために粘膜の血管の透見が困難となることもある．

食道に内視鏡検査で異常がみられるのは逆流性食道炎の70-80％程度であるとされているため，内視鏡検査で異常を認めるときはもちろん，異常がなくても好酸球性食道炎を思わせる症状がある場合には内視鏡下の生検を行うことが必要である．生検は生検個数が1個であれば診断の感度が50％にしかならないため複数カ所の生検が必要で，感度を100％にするためには5個以上の生検が必要であるとされる．また，好酸球性胃腸炎の可能性を否定するために胃粘膜と十二指腸粘膜の生検を同時に行って，これらの部位には異常な好酸球の浸潤がなく好酸球性胃腸炎ではないことを証明しておくことが必要である．好酸球性食道炎と診断するためには400倍の高倍率視野で1視野あたり15-20以上の好酸球が証明されることが必要である．

さらに，現在プロトンポンプ阻害薬(PPI)の投与で症状や食道粘膜への好酸球の浸潤が消失する例が30-50％程度存在することがわかっており，これらの例を好酸球性食道炎と診断せずにproton pump inhibitor-responsive esophageal eosinophilia(PPI-REE)と診断して別疾患として扱うべきであるという意見がある．ただし，好酸球性食道炎とPPI-REEを比較すると臨床像，内視鏡像，病理像，食道粘膜における遺伝子発現にほとんど差がなく同一疾患であると考えるべきであるとする意見もあり，今後の研究成果が注目されている[14]．

現在の厚生労働省の研究班の作製した好酸球性食道炎の日本での診断指針案を**表1**として示す．また，診断のフローチャート案を**図1**として示す．

鑑別診断が必要な疾患としては，逆流性食道炎，非びらん性胃食道逆流症，アカラシア，びまん性食道痙攣症，好酸球性胃腸炎，などを挙げることができる．

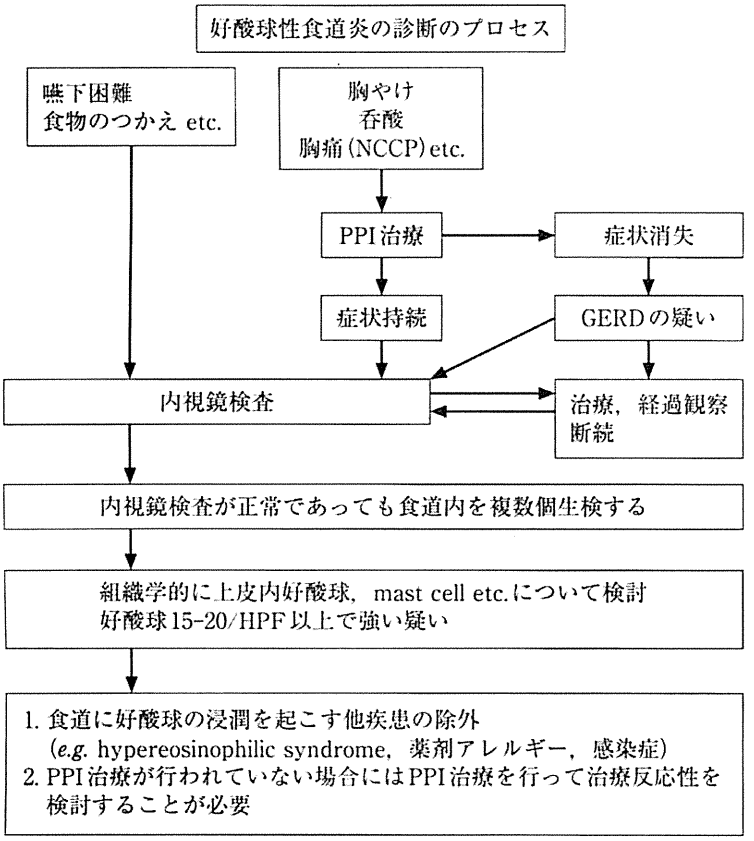

図1　好酸球性食道炎の診断フローチャート案

6. 治療と予後

好酸球性食道炎の治療の目的は嚥下障害や食事中の胸のつまり感を消失させHRQOLを改善することと，食道粘膜に長期炎症が持続し食道の線維化に伴う狭窄を予防することにある．治療は原因療法ともいえる食事療法，薬物療法のPPI投薬，グルココルチコイド製剤の投薬，食道狭窄に対するバルーン拡張術などがある．

1）食事療法

アミノ酸成分栄養食を用いて食物アレルゲンの摂取をなくすことで食道粘膜の好酸球浸潤を消失させることができる．コンプライアンスが悪いため，長期使用は困難で，寛解が得られた後に，戻し食を1食材ずつ行って原因食材を同定することが必要となる．

2）除去食

ミルク，小麦，卵，大豆，ナッツ，海産物の6種の食品を除いた食事をするよう指導をするのが最もよく行われている．栄養士の全面的なサポートが必要で成人で社会生活をしながら行うことは容易ではないが，小児では試みられる．

3）薬物療法

a. PPI

PPIの標準用量あるいは倍量を投薬することで2カ月程度で食道粘膜の好酸球浸潤が消失する例が30-50％程度にある．PPIでいったん消失した好酸球浸潤がPPI投薬中であるにもかかわらず再出現することも報告されているため経過観察を行う．寛解後，PPIを中止する時期に関しては十分な検討がない．PPIの副作用の少なさを考えると，まずこの治療を行ってみることが勧められる[15]．

b. 局所作用ステロイド

喘息の吸入療法に使用されているfirst passで肝臓で分解される局所作用ステロイドであるフルチカゾンやブデソニドを用いる．これらを口腔内に噴霧し唾液とともに嚥下することで食

道粘膜にステロイドを作用させながら全身性の副作用を最小限に抑えようとする治療である．好酸球性食道炎の標準的治療といえる．

c. 全身ステロイド

局所作用ステロイド治療でも効果が不十分な場合に用いられる．

4) 食道拡張術

食道の狭窄が出現したときに用いられる．バルーンカテーテルで狭窄部の拡張を行う治療である．日本では重症例が少ないためかほとんど行われていない．

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Allergology International 64 (2015) 253–259

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Original article

Racial differences in eosinophilic gastrointestinal disorders among Caucasian and Asian

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ARTICLE INFO

Article history:
Received 18 November 2014
Received in revised form
4 February 2015
Accepted 15 February 2015
Available online 30 March 2015

Keywords:
Asian
Caucasian
Eosinophilic esophagitis
Eosinophilic gastroenteritis
Eosinophilic gastrointestinal disorders

Abbreviations:
CI, Confidence interval; EGE, Eosinophilic gastroenteritis; EGID, Eosinophilc gastrointestinal disorders; EoE, Eosinophilic esophagitis; GI, Gastrointestinal; HPF, High-power field; IL, Interleukin; Th2, T-helper cell type2

ABSTRACT

Background: Although there is an increasing number of eosinophilic gastrointestinal disorders (EGID) cases including eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (EGE), being reported globally, no systematic reviews have been conducted to elucidate the racial differences in these disorders. We aimed to show the racial differences, especially among Caucasians and Asians, in the risk of EoE and EGE.

Methods: We conducted a systematic review using PubMed in September 2012. All case reports and case series on EGID that involved human subjects and described race or ethnicity, as well as pathological findings, were included. For the comparison of reported cases between Caucasians and Asians, a chi-squared test was used.

Results: Among the 687 studies found in PubMed, 121 studies fulfilled the eligibility criteria. In total, 2621 patients were reviewed. Among Caucasian EGID patients, 94% had EoE; while among Asian EGID patients, 72% had EGE ($p < 0.001$). Among EoE, Asians were significantly less likely to have dysphagia and heartburn, but more likely to have vomit and abdominal pain, compared to Caucasians ($p < 0.001$). Further, among EGE, Asians were significantly more likely to have eosinophil-infiltrated colon than Caucasians (OR: 3.22, 95% confidence interval [CI]: 1.60–7.04), but were less likely to have eosinophil-infiltrated stomach (OR: 0.29, 95% CI: 0.17–0.49).

Conclusions: We found that EoE occurs more frequently in Caucasian EGID patients than Asian EGID patients, while the reverse is true for EGE. Also, racial disparities in symptoms and eosinophil-infiltrated tissues were observed. Our findings suggest further genetic and environmental studies to elucidate the etiology of EGID.

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Introduction

Eosinophilic gastrointestinal disorders (EGID) are chronic inflammatory disorders characterized by primary eosinophilic infiltration of the gastrointestinal (GI) tract without any known causes of eosinophilia such as parasitic infections, drug reactions, and malignancy.[1] EGID include eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (EGE); EoE involves only the esophagus, while EGE involves any part of the GI tract.[1–3] These disorders have been gaining attention in recent years as several studies reported a rapid rise in their prevalence; in particularly EoE, which saw a 35-fold rise in Philadelphia, USA, and an 18-fold rise in Australia, over the past ten years.[4,5] However, the exact etiology of EGID has yet to be elucidated, although the role of food-derived antigen or inflammatory mediators such as IL-5, IL-13, thymic stromal lymphopoietin and eotaxin-3 have been described.[6–9]

Globally, there seems to be a disparity in the incidence rate of the type of EGID being reported; EoE cases have been reported more frequently in Western countries,[10–18] while EGE were more likely in Asian countries.[19–64] Although racial and ethnic disparities in the severity and prevalence of immune and allergic disorders such as asthma and atopic dermatitis have been demonstrated before,[65,66] no such association has not been evaluated for EGID. To that end, we conducted a systematic review on EGID, focusing on Caucasian and Asian populations.

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Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2015.02.003
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Methods

Literature reviews

All research articles involving human EoE or EGE cases, which described race or ethnicity, and pathological findings, were included for the study. Articles that were not published in English, had no abstract, or in the form of a review were excluded. A literature search was conducted on PubMed on 22nd September, 2012. The following search strings were used: "eosinophilic esophagitis" [All Fields], "allergic esophagitis" [All Fields], "eosinophilic esophagitis" [All Fields], "eosinophilic gastroenteritis" [All Fields], "allergic gastroenteritis" [All Fields]; together with the following search conditions: English [lang], NOT Review [ptyp], AND has abstract [text]. Initial eligibility screening based on title and abstract was performed independently in a standardized manner by two reviewers (Jun Ito and Takeo Fujiwara). Subsequently, a full-text screening was conducted for further assessment. Discrepancies between reviewers were resolved by consensus. Despite ethnicity not being clearly described in the literature, study subjects from South Korea, China, Taiwan, and Japan were regarded as Asian based on the ethnically homogenous nature of the countries.[67] If an identical set of subjects were used in multiple articles, the literature which had more detailed information or larger sample size was selected.

Analyses

Through full-text screening of eligible articles, we extracted and compiled patients' characteristics and clinical information. For single case reports or case series, information of each patient was recorded. If a study showed only aggregated sample characteristics and clinical information, aggregated data were used. Finally, we calculated total number of subjects and divided them by race, diagnosis, age and diagnostic criteria.

To stratify subjects by age, samples 18 years old or older were categorized as adults, while those less than 18 years old were categorized as children.[68] Samples from four studies which showed only aggregated sample data conducted in children's hospitals were assigned for the children category; two studies had mean age 6.4 and 11.4 years old, respectively,[69,70] and the other two involved samples of 18 and 21 years old, respectively.[71,72] One study which also showed only aggregated sample data with a 15-year-old patient among 42 EGE patients was assigned for the adult category, as the mean age of the samples was 48.2 years old, with the oldest patient being 72 years old.[43,68]

The difference in diagnostic criteria for EGID was considered as it may affect the number of reported cases. At present, a peak count of $\geq$15 eosinophils per high-power field (eos/HPF) is the minimum required threshold for the diagnosis of EoE,[73] with some studies using >20 or >24 eos/HPF.[4,8,74] In this review, EoE samples were divided into three groups based on either peak or mean number of eosinophils: $\geq$15 eos/HPF, >20 eos/HPF, and others or unknown. For EGE, no standards for diagnosis exist; however, the majority of studies on EGE follow a Talley criteria[75] which requires the presence of gastrointestinal symptoms and eosinophil infiltration of one or more areas of the gastrointestinal tract (with no evidence of parasitic or extraintestinal disease). In view of this, we divided EGE samples into two groups; one which met Talley's criteria, and the other one which neither meet the criteria nor mention the diagnostic criteria used.

A chi-squared test was used to compare the reported cases of EoE or EGE between Caucasians and Asians. Further, a logistic regression was conducted to calculate odds ratios (OR) of Asians who had GI symptoms (dysphagia, heartburn, vomit, abdominal pain and diarrhea), relative to Caucasians, among cases of EoE, EGE, and overall patients. The ORs of Asians who had eosinophilic infiltration for each GI tract (esophagus, stomach, small intestine and colon), relative to EGE Caucasians, were also calculated. All analyses were performed using the STATA SE statistical package, version 12 (Stata Corp., College Station, TX, USA).

Results

Our search identified 687 studies, of which 499 were deemed relevant on the basis of their titles and abstracts. Of these, 378 studies were subsequently excluded: 319 studies were without information on race or ethnicity; 46 studies had samples that were possibly duplicated; six studies had no pathological findings; six studies comprised of subjects whose diagnosis were not of EGID; and one study was a review article. Finally 121 studies were included for further analysis (Fig 1). The number of publications which included Caucasian patients and Asian patients was 59 and 70, respectively. In total, 2621 cases were obtained from these studies (Table 1). The cases included patients ranging from infant to elderly, with men more dominant for both EoE and EGE than women. Across all races, more than half of the EoE patients were diagnosed by the diagnostic criteria of >15 eos/HPF. For EGE, most Asian patients were diagnosed by Talley's criteria, while the same did not apply to Caucasians and other races. Among Caucasians, 94% of EGID patients had EoE, while among the Asian patients, 72% had EGE ($p < 0.001$).

There were significant differences in the number of reported cases of EoE and EGE between Caucasian and Asian samples (Table 2). Caucasian is dominant among EoE, while Asian is dominant among EGE for both in total and adult (both $p < 0.001$). For children, the percentage of Caucasian among EoE (97%) is higher than among EGE (68%) ($p < 0.001$).

Table 3 shows the odds ratios of Asians relative to Caucasians in having GI symptoms among EoE, EGE and EGID (i.e., considering total EoE and EGE cases). For esophagus related symptoms in EoE cases, Asians were 0.27 and 0.32 times less likely to have dysphagia and heartburn, respectively, than Caucasians (95% confidence interval [CI], 0.16–0.47; and 0.15–0.62, respectively). On the other hand, for stomach and lower GI tract related symptoms in EoE

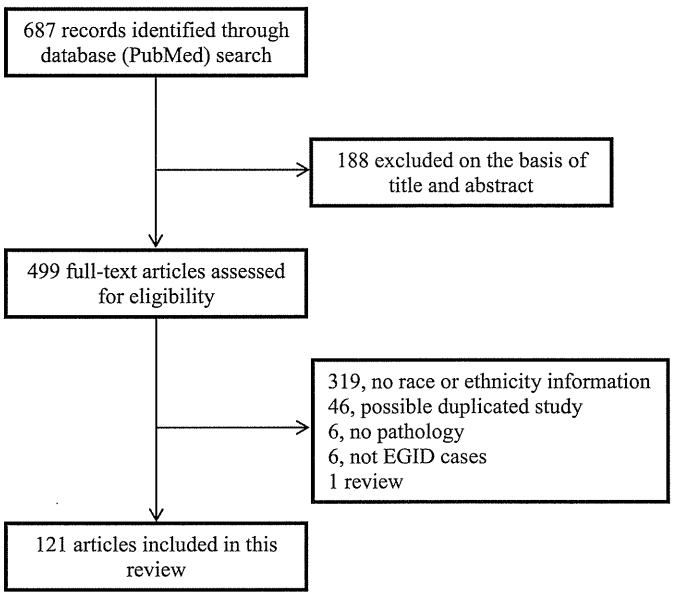

Fig. 1. Flow diagram of literature search.

Table 1
Characteristics of samples.

Race	Diagnosis	n (%)	†Age range	†Sex (male %)	Diagnostic criteria	n (%)	Reference
Caucasian	EoE	1873 (93.2)	15–76	70.9	eos >15 HPF	989 (52.8)	10–14,71,84–95
					eos >20 HPF	778 (41.5)	15,16,69,72,96–100
					unknown	106 (5.7)	17,18,70,101,102
	EGE	137 (6.8)	1–74	62.4	§Talley criteria	74 (54.0)	103–112
					unknown	63 (46.0)	113–129
Asian	EoE	105 (27.3)	11–83	70.4	eos >15 HPF	72 (68.6)	25,93–95,130–136
					eos >20 HPF	30 (28.6)	69,72,96,98,100,137–140
					unknown	3 (2.9)	101,141
	EGE	279 (72.7)	0–72	55.4	§Talley criteria	244 (87.5)	19–44,103
					unknown	35 (12.5)	45–64,117
‡Others	EoE	215 (94.7)	39	NA	eos >15 HPF	125 (58.1)	71,84–95
					eos >20 HPF	76 (35.3)	69,72,96–100
					unknown	14 (6.5)	70,101,102,142
	EGE	12 (5.3)	3–56	66.7	§Talley criteria	2 ((16.7)	143,144
					unknown	10 ((83.3)	57,117,120,145

EoE, eosinophilic esophagitis; EGE, eosinophilic gastroenteritis; eos, eosinophils; HPF, high-power field; NA, not applicable.
† Only studies whereby the majority of samples (>95%) consisted of either Caucasians or Asians were included.
‡ Other ethnicities include Latin American and African.
§ Presence of gastrointestinal symptoms and eosinophil infiltration of the gastrointestinal tract (with no evidence of parasitic or extraintestinal disease).

cases, Asians were 5.43 and 12.1 times more likely to have vomit and abdominal pain, respectively, than Caucasians (95% CI, 1.09–23.5; and 4.65–32.2, respectively). Among EGE cases, Asians were 0.32 times less likely to experience vomiting than Caucasians (95% CI, 0.19–0.54). In total cases, i.e. EGID cases, Asians were significantly less likely to have dysphagia and heartburn, and more likely to have vomit, abdominal pain and diarrhea.

Further, among EGE, Asians are 0.29 times significantly less likely to have the stomach infiltrated by eosinophils (95% CI, 0.17–0.49), while their colons are 3.22 times significantly more likely to be infiltrated by eosinophils (95% CI, 1.60–7.04) compared to those of Caucasians (Table 4).

Discussion

This systematic review revealed that among Asians, less EoE and more EGE cases were reported compared to Caucasians. Further, differences in GI symptoms were seen between Caucasians and Asians, even after stratification by EoE or EGE. Among EoE, Asians are significantly less likely to have dysphagia and heartburn directly related to the esophagus, but are significantly more likely to have vomit and abdominal pain relatively related to the stomach or the lower GI. Interestingly, among Asian EGE patients, the stomach is less likely to be infiltrated by eosinophils, hence less likely to experience vomiting than Caucasian EGE patients. Conversely, the colon in Asian EGE patients is more likely to be infiltrated by eosinophils, but lower GI symptoms are not significantly more likely to be seen compared to Caucasian EGE patients.

Helicobacter pylori infection is suspected to be one possible etiology of EGID because it affects immune response, especially Th2 response and Th2-related cytokines such as IL-5, 13, as well as eotaxins.[6–8] Recently, two cross-sectional studies showed an inverse association of EGID with *H. pylori*.[76,77] Thus, the prevalence of *H. pylori* infection might explain the racial differences with regards to the location of EGID (i.e. EoE or EGE). In Japan, the prevalence of *H. pylori* infection among the 55–64 age group was 88%, while that in the US was 35%.[78] Although a direct association between *H. pylori* infection and EGE is yet to be uncovered, the differences in prevalence and variation of the genotypes of *H. pylori* between races[79,80] may explain the racial disparities in the location of EGID. At the same time, *H. pylori* infection may partly explain why Asian EoE patients are less likely to experience heartburn. Gastroesophageal reflux can be seen as a concomitant cause for EoE, and there is an association of gastroesophageal reflux disease with a particularly virulent genotype of *H. pylori*.[81]

A diversity in dietary habits between the two races could be another possible explanation. According to the Food and Agriculture Organization of the United Nations, total vegetables supply quantity (kg/capita/yr) in Eastern Asia is more than double than that of Northern America, while total meat supply quantity in North America is more than double than that of Eastern Asia.[82] These dietary differences may be one reason of the variance of inflammatory site in the GI tract among races. Another possible explanation is that genetic polymorphism or epigenetic change in GI tract tissues may be associated with the racial differences in EGE. Further studies investigating racial differences and dietary habits, or immigration studies such as that of the Japanese acculturation among immigrants in Hawaii,[83] are warranted to elucidate the mechanism of higher predisposition of EGE among Asians.

To date, the diagnosis and treatment of EGE cannot be deduced as being more developed compared to EoE. As a greater area of the GI tract is impaired in EGE than in EoE, the QOL of EGE patients is more severely impacted, particularly in the form of malnutrition with hypoproteinemia. In addition, topical therapy with less side

Table 2
Reported cases of EoE and EGE among Caucasians and Asians.

Race	All samples			†Child (<18 y.o.)			‡Adult (≥18 y.o.)		
	EoE	EGE	§p value	EoE	EGE	§p value	EoE	EGE	§p value
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Caucasian	1873 (94.7)	137 (32.9)		1014 (97.0)	58 (68.2)		859 (92.1)	79 (23.9)	
Asian	105 (5.3)	279 (67.1)	<0.001	31 (3.0)	27 (31.8)	<0.001	74 (7.9)	252 (76.1)	<0.001

EoE, eosinophilic esophagitis; EGE, eosinophilic gastroenteritis.
† Samples of four studies from children's hospitals whereby the oldest age was not exactly 18 years old, or younger, were included.
‡ Samples of a study whose age range was from 15 to 72 years old were included.
§ Chi-squared test.

Table 3
Odds ratios of Asians having GI symptoms among EoE and EGE patients, respectively, relative to Caucasian.

	Dysphagia		Heartburn		Vomit		Abdominal pain		Diarrhea	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
EoE										
†Caucasian (n = 552)	426 (77.2)	reference	215 (38.9)	reference	6 (1.1)	reference	10 (1.8)	reference	5 (0.9)	reference
†Asian (n = 71)	34 (47.9)	0.27 (0.16–0.47)*	12 (16.9)	0.32 (015–0.62)*	4 (5.6)	5.43 (1.09–23.5)*	13 (18.3)	12.1 (4.65–32.2)*	0 (0)	NA
EGE										
†Caucasian (n = 92)	5 (5.4)	reference	3 (3.3)	reference	44 (47.8)	reference	61 (66.3)	reference	44 (47.8)	reference
†Asian (n = 276)	15 (5.4)	1.00 (0.33–3.62)	3 (1.1)	0.33 (0.04–2.49)	62 (22.5)	0.32 (0.19–0.54)*	179 (64.9)	0.94 (0.55–1.58)	138 (50.0)	1.09 (0.66–1.80)
Total										
†Caucasian (n = 644)	431 (66.9)	reference	218 (33.9)	reference	50 (7.8)	reference	71 (11.0)	reference	49 (7.6)	reference
†Asian (n = 347)	49 (14.1)	0.08 (0.06–0.12)*	15 (4.3)	0.09 (0.05–0.15)*	66 (19.0)	2.79 (1.85–4.23)*	192 (55.3)	10.0 (7.14–14.0)*	138 (39.8)	8.02 (5.51–11.8)*

CI, confidence interval; EoE, eosinophilic esophagitis; EGE, eosinophilic gastroenteritis; GI, gastrointestinal; NA, not applicable; OR, odds ratio.
† Only studies in which the majority of samples (>95%) consisted of either Caucasians or Asians were included.
* $p < 0.05$.

Table 4
Odds ratios of Asian EGE patients having eosinophilic infiltration in the esophagus, stomach, small intestine and colon, relative to Caucasian EGE patients.

	Esophagus		Stomach		Small intestine		Colon	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
†Caucasian (n = 92)	4 (4.3)	reference	59 (64.1)	reference	48 (52.2)	reference	11 (12.0)	reference
†Asian (n = 276)	17 (6.2)	1.44 (0.45–6.05)	95 (34.4)	0.29 (0.17–0.49)*	166 (60.1)	1.38 (0.84–2.28)	84 (30.4)	3.22 (1.60–7.04)*

CI, confidence interval; EGE, eosinophilic gastroenteritis; OR, odds ratio.
† Only studies in which the majority of samples (>95%) consisted of either Caucasians or Asians were included.
* $p < 0.05$.

effects, such as proton-pump inhibitor, fluticasone and budesonide, cannot be used for EGE. At present, the effects of dietary treatment, a potent therapeutic method for EoE, are not fully understood for EGE patients. Hence, there is a crucial need for guidelines for diagnosis and treatment of EGE. At the same time, clinicians who tend to EGID patients should consider the race and the country of residence of the patients, as the affected area within the GI tract may vary accordingly.

Several limitations to this study need to be addressed. First, the diagnostic criteria and the quality of diagnosis were not unified. Hence, there may be potential misclassification. According to the consensus recommendation of EoE diagnosis, biopsy specimens should be obtained not only from various esophageal locations along the length of the esophagus, but also from the lower GI tract, to rule out other diseases.[73] However, we found that not all studies clearly stated all of the biopsy sites. In view of that, we are aware that there may be cases that are not true EoE. For the diagnosis of EoE, there are two major criteria for eosinophil counts. As shown in Table 1, 41.5% of the Caucasian and 28.6% of the Asian EoE patients were diagnosed by a more stringent criteria of 20 eos/HPF. As such, there would have been patients who had EoE, but had eosinophil counts of between 15 and 19 eos/HPF, being excluded from the reports. In spite of that, this possible misclassification does not affect our finding of Caucasians being more likely to have EoE than Asians. In fact, it would further affirm our results.

Second, some studies did not report EoE or EGE cases stratified by racial groups. As we selected studies in which the major racial composite (>95%) of the samples was either that of Asians or Caucasians, there may be a certain degree of misclassification in terms of race. However, the number of such cases was small (n = 6). Therefore, the effect of this misclassification is negligible.

In conclusion, we have demonstrated through a systematic review that EoE is more likely to exist among Caucasian EGID patients than such patients of Asian descent, while the reverse is true for EGE. Symptoms and eosinophil-infiltrated tissues related to the esophagus are more likely to be found among Caucasian EGID patients, while symptoms and eosinophil-infiltrated tissues related to the stomach or the lower GI tract are frequent in Asian EGID patients. These findings warrant further genetic and environmental studies for the etiology of EGID. Furthermore, investigations from the viewpoint of *H. pylori* infection, dietary habits, and genetic predisposition using genome-wide association study, can be valuable in elucidating the etiology of EGID.

Acknowledgment

We would like to thank Dr. Julian Tang of the Department of Education for Clinical Research, National Center for Child Health and Development, for proofreading and editing this manuscript. This study was supported by a grant from the Ministry of Health, Labour and Welfare of Japan, Research for Intractable Diseases, (H26-nanchi-ippan-048) to I.N.

Conflict of interest
The authors have no conflict of interest to declare.

Authors' contributions
TF and IN conceived and designed the study, JI conducted systematic review, JI and RK collected data, JI analyzed and wrote the first manuscript, TF and IN finalized the manuscript. All authors read and approved the final manuscript.

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Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.12746

ORIGINAL ARTICLE

Clinical features of eosinophilic esophagitis: Differences between Asian and Western populations

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Key words
Asian populations, endoscopic findings, eosinophilic esophagitis, epidemiology, esophageal eosinophilia.

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Conflicts of interest: No conflicts of interest to disclose.

Abstract

The prevalence and incidence of eosinophilic esophagitis (EoE) have been rapidly increasing in Western countries. It is thought to be more common among Caucasians than other racial or ethnic groups, but epidemiological studies have not been fully evaluated in Asian populations, and its clinical manifestation is rarely documented. In this review, recent reports regarding EoE in Asian countries have been collected, and differences in the clinical features, including symptoms and endoscopic findings, between Asian and Western populations have been evaluated. In Asia, EoE is still much less prevalent than in Western countries. Baseline values for average age, male/female ratio, and personal history of allergic disease were comparable to those in Western populations. Predominant symptoms were dysphagia, and food impaction was extremely rare among Asian patients. Although the frequency of abnormal endoscopic findings varies among studies, over 90% of patients with EoE have shown abnormal findings such as linear furrow, which is the most common findings, in recent prospective studies in Asia. There are few reports regarding the treatment of EoE and no prospective studies evaluating drugs or elimination diet in patient with EoE have been reported in Asia. Overall, EoE had similar clinical characteristics in Asian populations. Because the incidence of EoE could increase in the future with the increase in allergic disorders in Asian countries, large-scale, nationwide prospective studies should be performed to more fully understand the epidemiology and pathophysiology of EoE in Asian populations.

Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder characterized by dense eosinophilic infiltration of the esophageal epithelium without infiltration of other parts of the gastrointestinal tract.[1,2] It is a relatively new disease entity first described by Landres *et al.* in 1978,[3] and increasingly recognized over the past decade. The incidence and prevalence of EoE have been rapidly increasing, especially in Western countries,[4,5] and it has become a major cause of gastrointestinal morbidity among children and adults. Cases of EoE have been reported from all continents except Africa. The clinical characteristics of EoE have been extensively investigated in Western countries, but not other countries.[2,6] The first case of a Japanese patient with EoE was reported in 2006.[7] Since then, it appears that cases of EoE are increasingly reported from other Asian countries, including South Korea,[8] China,[9] Thailand,[10] India,[11] Turkey,[12] and Saudi Arabia.[13] However, the disease is recognized as a rare condition and its epidemiology has not been fully estimated in Asia.

EoE is clinicopathological disease that is diagnosed by symptoms related to esophageal dysfunction accompanied by more than 15 intraepithelial eosinophils/high-power field (HPF) in at least one biopsy specimen without pathogenesis of gastroesophageal reflux disease (GERD) as shown by lack of response to high-dose proton-pump inhibitor (PPI) medication.[14,15] The presenting symptoms in patients with EoE can differ between children and adults.[16] Children often have symptoms of feeding intolerance, vomiting, and failure to thrive, while adults usually have symptoms of dysphagia, food impaction, heartburn, and chest pain. Moreover, a variety of clinical features by racial and ethnic differences have been reported. Solid food dysphagia is reported to be more common among white patients, whereas reflux symptoms are more common in black/Hispanic patients.[17] On the other hand, Sperry *et al.* reported that the majority of symptoms, endoscopic findings, and histological features were not different between Caucasians and African American subjects.[18] It remains to be elucidated if there is a difference between Asian and non-Asian populations because most current knowledge about EoE in Asian population is based on case reports and small case series. However, it is of importance to identify the clinical features, including presenting symptoms and endoscopic findings, in Asian populations in the context of growing recognition of EoE widely in Asia.

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We review the present status of EoE in Asia and discusses the differences in the clinical features of Asian and Western populations.

Epidemiology

Prevalence. The prevalence of EoE varies on the basis of study design and setting, and most of the studies have reported from Western countries. In the general population, case estimates have ranged from 0.2 to 4/1000 in asymptomatic patients,[5,19,20] but in those undergoing endoscopy for upper gastrointestinal (UGI) symptoms, EoE is found in 5–16%.[4,21,22] Current estimates suggest that the overall prevalence of EoE in Western population is between 43 and 56.7/100 000.[23–25] In Japan, the first EoE case was reported by Furuta *et al.*[7] in 2006, and since then the cases have been reported increasingly.[26,27] Likewise, the number of case reports regarding EoE in other Asian countries has been gradually increasing from 2009.[8,10,11,13] To date, nine epidemiological studies have been conducted in Asian countries (Table 1). The first prospective study carried out in 23 346 patients who had underwent routine esophagogastroduodenoscopy (EGD) in Japan estimated 0.02% (17.1/100 000),[28] which was much lower than the reports from Western countries. These data indicate that EoE could be found in approximately 1 in 5000 endoscopy-investigated cases. Consistently, studies have reported that the prevalence of EoE ranges from 0.01% to 0.13% in patients who undergo EGD.[32–34] There have been a few studies evaluating the presence of EoE in patients with UGI symptoms, such as dysphagia and heartburn. A prospective Korean study reported a prevalence of EoE among patients with esophageal or UGI symptoms as 6.6% (8/122).[30] In a Turkish study, the frequency of EoE in patients with esophageal symptoms was 2.6% (8/311).[31] We recently evaluated the prevalence of esophageal eosinophilia (EE), which is a pathological hallmark of EoE, among esophageal symptoms and found eight patients (2.5%) among 319 with esophageal symptoms.[35] These data indicate that the prevalence of EoE with UGI symptoms may not be so low as compared with Western countries. The mean age at diagnosis of EoE in adults ranges from 40 to 63 years, so it is frequently observed in middle-aged persons (Table 2). The difference is a somewhat older age of Asian patients with EoE as compared with Western patients.[38] Similar to Western reports, EoE is more common in males (50–100%). Only one study of the prevalence of EoE in children has been reported, from Saudi Arabia in 2012.[29] That study found 18 patients among 2127 EGD cases for UGI symptoms who were diagnosed as EoE, constituting 0.85% of the total number of patients. The prevalence of EoE in children has never been reported in East Asian countries. Collectively, EoE and EE are still rare in the general Asian population, but clinicians should be aware of EoE in patients with UGI symptoms.

Allergic status. EoE is considered to be an allergy-associated inflammatory disorder, possibly caused by antigens in the air and food. Indeed, cases of EoE are frequently associated with atopic disorders, as affected individuals often have coexistent bronchial asthma, allergic rhinitis, atopic dermatitis, and various food or drug allergies.[39,40] The frequency of allergic diseases in patients with EoE as a comorbidity in Asian populations

Table 1 Prevalence of EoE and EE in Asian countries

Study (published year)	Study period	Country	Study method (adults/children)	Sample size	No. of patients (M/F)	Prevalence
Fujishiro *et al.*[28†] (2011)	2010	Japan	Multicenter, prospective (adults)	23 346 (endoscopy cases)	4 (2/2)	0.02%(17.1/100 000)
Saadah *et al.*[29] (2012)	2002–2011	Saudi Arabia	Multicenter, retrospective (children; < 18 years)	2 127 (endoscopy cases)	18 (13/5)	0.85%
Joo *et al.*[30] (2012)	2009	South Korea	Single center, prospective (adults)	122 (UGI symptoms)	8 (5/3)	6.6%
Shi *et al.*[9†] (2012)	2006–2010	China	Single center, retrospective (adults)	3 490 (esophageal biopsy cases)	12 (7/5)	0.34%
Altun *et al.*[31] (2013)	2010–2011	Turkey	Single center, prospective (adults)	311 (UGI symptoms)	8 (4/4)	2.6%
Fujiwara *et al.*[32†] (2012)	2010–2011	Japan	Multicenter, prospective (adults)	13 634 (endoscopy cases)	7 (7/0)	0.05% (EE)
						0.01% (EoE)
Tomomatsu *et al.*[33†] (2013)	2010–2011	Japan	Single center, retrospective (adults)	7 557 (endoscopy cases)	10 (7/3)	0.13%(132.3/100 000)
Hori *et al.*[34] (2014)	2010–2012	Japan	Single center, prospective (adults)	2 545 (endoscopy cases)	2	0.08%
Shimura *et al.*[35†] (2014)	2011–2012	Japan	Multicenter, prospective (adults)	319 (UGI symptoms)	8 (4/4)	2.5%

†Including cases of PPI-responsive esophageal eosinophilia.
EE, esophageal eosinophilia; EoE, eosinophilic esophagitis; PPI, proton-pump inhibitor; UGI, upper gastrointestinal.

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Table 2 Characteristics and clinical presentation of adult patients with EoE and EE in Asia

Study	Year	Country	No. of patients	Age, years		Male sex		Heartburn	Dysphagia	Food impaction	Allergy
				Mean	Range	*n*	%	*n*	*n*	*n*	*n*
Abe *et al.*[26†]	2011	Japan	12	47.7	32–68	9	75	1 (8.3%)	7 (58.3%)	0	3 (25%)
Fujishiro *et al.*[28†]	2011	Japan	4	63.3	51–83	2	50	2 (50%)	1 (25%)	1 (25%)	NR
Joo *et al.*[30]	2012	South Korea	8	41.1	25–61	5	62.5	4 (50%)	3 (37.5%)	2 (25%)	NR
Shi *et al.*[9†]	2012	China	12	51.4	29–71	7	58.3	2 (16.7%)	4 (33.3%)	0	NR
Altun *et al.*[31]	2013	Turkey	8	40.2	27–52	4	50	7 (87.5%)	1 (12.5%)	0	3 (37.5%)
Fujiwara *et al.*[32†]	2012	Japan	7	50.3	37–70	7	100	3 (42.9%)	(3)‡	(3)‡	4 (57.1%)
Tomomatsu *et al.*[33†]	2013	Japan	10	47.5	26–73	7	70	3 (30%)	4 (40%)	2 (20%)	9 (90%)
Kinoshita *et al.*[36†]	2013	Japan	26	49	25–70	20	76.9	2 (7.7%)	12 (46.2%)	0	13 (50%)
Lee *et al.*[37†]	2013	South Korea	8	40.0	19–60	6	75	1 (12.5%)	6 (75%)	0	5 (62.5%)
Shimura *et al.*[35†]	2014	Japan	12	49.3	24–82	7	58.3	4 (33.3%)	5 (41.7%)	0	3 (25.0%)

†Including cases of PPI-responsive esophageal eosinophilia.

‡Cases of dysphagia or food impaction.

EE, esophageal eosinophilia; EoE, eosinophilic esophagitis; NR, not reported; PPI, proton-pump inhibitor.

is shown in Table 2. Although the association of a history of allergic diseases and EoE varies among studies because of small sample sizes, approximately half of the Asian patients have a history of allergic disease that is similar to reports from Western populations.

Foods have been shown to be an important cause of EoE through the use of elimination diets or elemental formulas in both pediatric and adult patients.[41,42] On the other hand, seasonal variation in esophageal mucosal eosinophilia and incidence is described, suggesting a correlation with seasons of more intense allergen exposure.[43–45] Although patients with EoE are frequently positive for allergy testing such as skin prick test and serum antigen-specific IgE antibody, the clinical significance of these tests for management of EoE remains controversial. Both laboratory-based research and clinical studies have indicated a strong role for the non-IgE-mediated T-helper 2 (Th2)-delayed hypertensive response in EoE.[46,47] Therefore, the usefulness of allergy testing for EoE may be limited. Indeed, Gonsalves *et al.* recently demonstrated that skin prick testing predicted only 13% of food-associated cases of EoE.[41] Because there are no reports evaluating the efficacy of food elimination diets for patients with EoE in Asian countries, it remains unclear how food and/or aeroallergens affect patients with EoE in Asia. We have recently evaluated the possible involvement of food and/or aeroallergen factors in EoE using serum antigen-specific IgE antibodies in a Japanese population.[48] Consistent with the higher levels of serum total IgE antibodies, patients with EoE were frequently sensitized to multiple antigens. However, no particular antigen causing EoE was detected by measuring serum antigen-specific IgE antibodies.

Helicobacter pylori *infection.* Reduced exposure to microorganisms during childhood may result in failure to activate the Th1 immune response, leading to an imbalance between the Th1 and Th2 immune responses and a predisposition to develop allergic disorders that are triggered by altered or missing innate immune cell activation. This concept is termed the "hygiene hypothesis"[49] and provides a general explanation for the increase in allergic diseases, including EoE, parallel to the decrease in infectious diseases. Of note, early life exposure to *H. pylori* infection has been inversely associated with conditions such as asthma and allergic rhinitis,[50–52] and a decrease in *H. pylori* infections may predispose individuals to various allergic diseases. Recent study has suggested that *H. pylori* infection is inversely associated with EE.[53] However, there are few reports of the relationship between EoE and *H. pylori* infection in either Western or Asian populations.[54] Furuta *et al.* recently investigated the possible influence of *H. pylori* infection on EoE in Japanese patients by case–control study.[55] In that study, 22.3% of the patients with EoE were infected with *H. pylori*, as compared with 55.5% of their age- and sex-matched healthy controls. The odds ratio for EoE patients to have *H. pylori* infection was 0.22, which was significantly lower in EoE and consistent with reports regarding other allergic diseases. Because the recent increase in EoE might be related not only to *H. pylori* infection, but also to changes in the social environment,[25] large-scale and multicenter studies should be carried out to further determine the relation between *H. pylori* and allergic disorders.

Diagnosis

Symptoms. EoE is one of most the common causes of intermittent solid-food dysphagia or food impaction in adults in Western countries. In 10 studies evaluating the symptoms of patients with EoE in Asia, the most common presenting symptom was dysphagia (Table 2). Interestingly, food impaction was very rare in contrast to Western reports. Moreover, most of the Asian reports show no severe progressive cases, such as complete obstruction or long segment obstruction. We recently demonstrated that none of the presenting symptoms, including dysphagia, heartburn, and chest pain, was useful for diagnosis of EoE by logistic regression analysis.[35] Consistently, Mackenzie *et al.* prospectively assessed the risk factors and prevalence of EoE in an adult population with dysphagia.[21] Of 261 patients enrolled, 31 (12%) met the pathological criteria for EE, but EE was found only in five cases (1.9%) with normal endoscopic findings, suggesting that endoscopic abnormal findings suspicious of EoE are more important and effective for predicting EoE than esophageal symptoms.

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Table 3 Endoscopic findings of adult patients with EoE and EE in Asia

Study	Year	Country	No. of patients	Abnormal EGD findings	Type of findings			Normal EGD findings
					Linear furrows	Rings	Whitish exudate	
Abe *et al.*[26†]	2011	Japan	12	11 (91.7%)	10 (83.3%)	10 (83.3%)	9 (75%)	1 (8.3%)
Fujishiro *et al.*[28†]	2011	Japan	4	4 (100%)	2 (50%)	1 (25%)	3 (75%)	0
Joo *et al.*[30]	2012	South Korea	8	6 (75%)	2 (25%)	2 (25%)	3 (37.5%)	2 (25%)
Shi *et al.*[9†]	2012	China	12	9 (75%)	1 (8.3%)	1 (8.3%)	1 (8.3%)	3 (37.5%)
Altun *et al.*[31]	2013	Turkey	8	4 (50%)	0	2 (25%)	2 (25%)	4 (50%)
Fujiwara *et al.*[32†]	2012	Japan	7	7 (100%)	6 (85.7%)	3 (42.9%)	3 (42.9%)	0
Tomomatsu *et al.*[33†]	2013	Japan	10	10 (100%)	10 (100%)	3 (30%)	6 (60%)	0
Kinoshita *et al.*[36†]	2013	Japan	26	15 (57.7%)	9 (34.6%)	5 (19.2%)	6 (23.1%)	11 (42.3%)
Lee *et al.*[37†]	2013	South Korea	8	7 (87.5%)	6 (75%)	4 (50%)	0	1 (12.5%)
Hori *et al.*[34†]	2014	Japan	5	5 (100%)	3 (60%)	3 (60%)	2 (40%)	0
Shimura *et al.*[35†]	2014	Japan	12	11 (91.7%)	10 (83.3%)	3 (25.0%)	4 (33.3%)	1 (8.3%)

†Including cases of PPI-responsive esophageal eosinophilia.
EE, esophageal eosinophilia; EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; PPI, proton-pump inhibitor.

Endoscopic findings. There are a number of reports of the endoscopic features of EoE in Western patients, which include esophageal rings, linear furrows, whitish exudates, and stenosis.[56,57] Endoscopic findings may differ by race. Bohm *et al.* reported that normal endoscopy and reflux changes were more common in black/Hispanic patients, whereas linear furrows and rings were more common in white patients.[17] Eleven studies have evaluated the endoscopic features of patients with EoE in Asia (Table 3). In most of them, > 75% of patients with EoE had abnormal endoscopic findings. In contrast, according to the report with the largest number of EoE cases in Asia, 11 (42.3%) of 26 patients had a normal-appearing esophagus.[36] The study was based on a questionnaire administered to patients with EoE who had been diagnosed from 2004 to 2009. Thus, the results may reflect a lack of awareness of the disease because most of the Asian studies have been published since 2011. According to a recent meta-analysis, in prospective studies, at least one abnormality was detected by endoscopy in 93% of EoE patients.[58] Consistent with that, more recent prospective studies conducted in Japan have shown endoscopic abnormalities in 91.7% to 100% of the patients with EoE.[32–35] In those studies, linear furrows were the most frequently found endoscopic abnormality in patients with EoE and/or EE, suggesting that endoscopic abnormal findings suspicious of EoE, especially linear furrows, can be detected in most of the patients with EoE by experienced endoscopists with careful observation using a high-resolution endoscope or narrow band imaging endoscopy[59] (Fig. 1). Miller *et al.* reported that upper endoscopy with biopsy for EoE appears to be a cost-effective approach in patients when the prevalence of EoE is 8% or greater.[60] Thus, a biopsy may not be recommended for the evaluation of patients with esophageal symptoms but no endoscopic abnormalities.

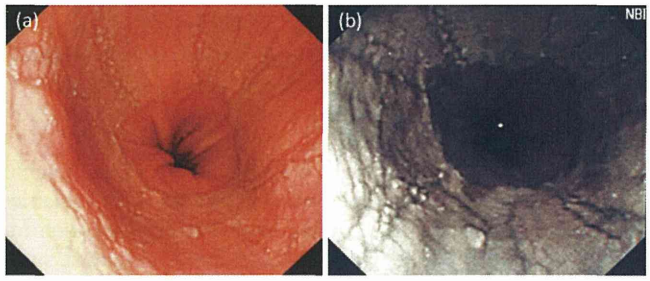

Figure 1 Endoscopic finding of linear furrows in patients with eosinophilic esophagitis. (a) Conventional endoscopy and (b) narrow-band imaging endoscopy.

Cytokine expression. The results of genome-wide association study (GWAS) have implicated the 5q22 locus in the pathogenesis of EoE and identify thymic stromal lymphopoietin (*TSLP*) as the most likely candidate gene in the region.[61] TSLP is an interleukin (IL)-7-like cytokine that is a critical factor linking responses at interfaces between the body and environment (skin, airway, gut, ocular tissues, etc.) to Th2 responses. Stimulated Th2 lymphocytes produce IL-5 and IL-13, and dendritic cells produce IL-15. Then, IL-13 and IL-15 increase eotaxin-3 production by esophageal epithelial cells. Eotaxin-3 is a potent chemokine that facilitates the trafficking of eosinophils from peripheral blood to the esophageal epithelium. Moreover, genetic polymorphism in the human gene *CCL26* (eotaxin-3) has been found to be associated with increased susceptibility for EoE.[62] Indeed, patients with EoE have been reported to have higher concentrations of these cytokines in peripheral blood than normal individuals.[46,63,64] However, the expression of these cytokines in patients with EoE in Asian populations has not been fully evaluated. Kinoshita *et al.* investigated plasma concentrations of these cytokines (TSLP, IL-5, IL-13, IL-15, eotaxin-3) in 18 Japanese EoE patients.[65] Consistent with previous reports, they found that plasma concentrations of IL-5 and IL-15 were significantly higher in EoE patients as compared with healthy controls. Although the diagnostic value of cytokine measurement is limited because of the large overlap between patients and controls, the similar responses suggest a similar role for these cytokines in EoE in both Asian and Western populations. Likewise, a single nucleotide polymorphism in the TSLP locus has been reported to be associated with adult asthma in populations of both Japanese and non-Hispanic individuals of European ancestry.[66] GWAS of EoE in Asian populations is needed for future research.

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Table 4 Treatment of adult patients with EoE and EE in Asia

Study	Year	Country	No. of patients	PPI responsive	PPI non-responsive			No treatment
					Topical steroid	Oral steroid	Others	
Abe *et al.*[26†]	2011	Japan	12‡	5	2	0	0	3
Fujishiro *et al.*[28†]	2011	Japan	4	2	1	0	0	1
Shi *et al.*[9†]	2012	China	12‡	7	—	—	—	3
Fujiwara *et al.*[32†]	2012	Japan	7	3	1	0	1	2
Tomomatsu *et al.*[33†]	2013	Japan	10	2	0	3	1	4
Kinoshita *et al.*[36†]	2013	Japan	26	4	(16)§	(16)§	—	4
Lee *et al.*[37†]	2013	South Korea	8	4	0	3	0	1

†Including cases of PPI-responsive esophageal eosinophilia.
‡Two cases not treated by PPI.
§Sixteen cases treated either by topical or oral steroid.
—, data not shown; EE, esophageal eosinophilia; EoE, eosinophilic esophagitis; PPI, proton-pump inhibitor.

Treatment

At present, there is no standardized treatment for EoE, and different therapeutic regimens have been used for patients with EoE in Asia. Treatment for EoE has been described in seven case series studies (Table 4). Importantly, all these studies included PPI-responsive symptomatic patients with esophageal eosinophilic infiltration greater than 15–20 eosinophils/HPF, possibly because of the small sample sizes. This condition is referred to as "PPI-responsive esophageal eosinophilia" (PPI-REE),[14,15] and is diagnosed when a trial of PPI improves symptoms and eosinophilic infiltration in patients with clinical characteristics similar to EoE.[67,68] Initially, PPI-REE was considered to be a separate entity from EoE. To distinguish EoE from other causes of EE, including GERD and PPI-REE, the guideline strongly recommends that patients with suspected EoE should be given a 2-month course of a PPI followed by endoscopy with biopsies. However, as EoE has become more widely recognized, it has also become increasingly evident that the distinction between EoE and GERD is not always clear.[69,70] Moreover, the pathogenesis of PPI-REE remains unclear.[71] Because of the potential mechanism that gastric acid plays a role in the pathogenesis of EoE and that PPIs have anti-inflammatory actions independent of their effects on gastric acid secretion,[72–74] EoE patients might benefit from PPI therapy whether or not they have coexisting GERD. More studies are sorely needed to recognize, define, and mechanistically understand PPI-REE.

As for PPI non-responsive patients diagnosed as having typical EoE, topical or oral steroids have been used as treatment in several cases. Because of the rareness of EoE patients with food impaction or other severe complications in Asia, intensive treatment such as esophageal dilatation or surgical operation has not been reported. Administration of steroid has been effective for most of the patients with EoE regarding symptoms and endoscopic findings; however, prognosis remains obscure. Although oral topical steroids can be effective in limiting EoE-associated inflammation, there are concerns regarding the long-term use of steroids, particularly in children. Adherence to an elemental diet that eliminates exposure to foods that trigger EoE results in resolution of symptoms in many patients; however, this approach requires disruptive changes in lifestyle and eating habits. The effect of elimination diet therapy remains to be elucidated in Asia. Thus, there is a need to identify the effect of diet therapies for Asian patients, who have different dietary habits from those in Western countries.

Conclusion

The findings of a thorough review of the medical literature reported in Asian countries suggest that EoE affects middle-aged men who have an allergic predisposition that is similar to the clinical features of patients in Western populations. Dysphagia is a more common symptom than food impaction, and the complication of food bolus obstruction has not been reported, suggesting that the clinical presentation of EoE in Asian patients is milder than in Western patients. Typical endoscopic findings include linear furrows, rings, and whitish exudates. Most of the recent studies have shown endoscopic abnormalities in over 90% of patients with EoE in Asia. Although case series have been reported increasingly, larger scale, nationwide studies should be performed in Asian populations.

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