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表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
池田　均	ストーマ・排泄管理の歴史	溝上祐子、池田　均	小児創傷・オストミー・失禁管理の実際	照林社	東京	2010	7-10
池田　均	日本の小児ストーマの現状	溝上祐子、池田　均	小児創傷・オストミー・失禁管理の実際	照林社	東京	2010	11-14

雑誌

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Ⅳ. 研究成果の代表的論文

Eosinophilic gastrointestinal disorders (EGIDs) in infants - A Japanese case series

Running head: EGIDs in infants

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Abstract

Background: Eosinophilic gastrointestinal disorders (EGIDs) are disorders characterized by primary eosinophil inflammation in the gastrointestinal tract. There are a small number of reports of eosinophil infiltration in gastrointestinal tracts as EGIDs in infants. In this study, we presented Japanese cases of EGIDs in infants. **Methods:** Five patients diagnosed or strongly suspected as having EGIDs in our hospital from 2008 to 2010 were reviewed. Radiographic contrast enema examinations and/or endoscopies were performed in 4 patients and 3 patients, respectively. **Results:** There were patients with eosinophilic colitis (1 suspected and 2 biopsy-proven), a patient who was suspected of having allergic eosinophilic enterocolitis and a patient with eosinophilic gastroenteritis associated with pediatric hypereosinophilic syndrome (HES). **Conclusions:** The causes and clinical findings of patients with intestinal eosinophil inflammation vary. Therefore, deliberate examination and observation are important for patients with infantile EGID.

Introduction

Eosinophilic gastrointestinal disorders (EGIDs), including eosinophilic esophagitis (EE), eosinophilic gastritis, eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC), were originally defined as disorders that primarily affect the gastrointestinal tract with eosinophil inflammation to the exclusion of those secondary diseases caused by drug reactions, parasitic infections, and malignancy [1]. Biopsy is the only way to definitively diagnose EGIDs [1]. Most patients with EGIDs are atopic and EGIDs are considered to have properties that fall between IgE-mediated allergies and cellular-mediated hypersensitivity disorders, although EC occurs mostly through a non-IgE-mediated mechanism [1]. In western countries, EE is increasingly diagnosed across all age groups and attracts much attention [2]. On the other hand, eosinophil infiltration in the lower gastrointestinal tract is mostly described as a histological finding of allergic diseases such as food protein-induced proctocolitis (FPIP), whose diagnosis is generally made clinically; therefore, only a small number of series have focused on biopsies [3]. In addition, unlike eosinophilic (procto)colitis, EGE is solely categorized as a disease that generally affects children and young adults, meaning that it is rare in infants [4]. Here, we present a case series of EGIDs in infants, including a rare case associated with pediatric hypereosinophilic syndrome (HES).

Patients and Methods

Patients

During a 2-year period (from June 2008 to May 2010) at Gunma Children's Medical Center, 5 patients were diagnosed or strongly suspected as having EGIDs. The patients were clinically examined by the pediatricians or pediatric surgeons and blood for the analysis of total and differential white blood cell count, levels of IgE, allergen-specific IgE, and the allergen-lymphocyte stimulation test (ALST), as well as fecal samples, were obtained. ALST was performed using LPS-depleted cow's milk proteins at the National Research Institute for Child Health and Development, Tokyo, Japan. Fecal samples were applied on a glass slide either directly or using cytospin, and the slides were then stained with May-Giemsa staining [5].

Radiographic examinations and endoscopies

Four out of 5 patients had a radiographic contrast enema examination. Upper gastrointestinal endoscopy or colonoscopy was performed on 1 and 2 patients, respectively, under general anesthesia. Biopsy specimens for morphology were fixed in phosphate-buffered formalin and embedded in paraffin blocks by using standard methods. Paraffin sections were stained routinely with hematoxylin and eosin and reviewed by a pathologist [6].

Elimination and provocation test

Open cow's milk challenge testing was performed after rectal bleeding disappeared during an elimination diet and the subjects had had good daily weight gain with no demonstration of symptoms [7]. We carefully observed the patients for up to 2 weeks while increasing their intake of milk.

Results

Case 1: A 8-month-old boy who had a congenital syndrome characterized by iris coloboma, ptosis, hypertelorism, and mental retardation, described as Baraitser–Winter syndrome (BWS) [8], was admitted to the allergy and immunology department in our hospital for generalized edema and coldness of limbs, along with exacerbation of full-body eczema. The patient had presented with severe eczema and peripheral blood hypereosinophilia and had been treated with supportive measures since he was a newborn infant. He often had vomiting and loose stool. He was a mixed-fed infant and had never been examined in relation to allergy, elsewhere. On admission, he had peripheral blood leukocytosis with sever hypereosinophilia and granulocytic immature cells (myelocytes and metamyelocytes), hypoproteinemia, and hyponatremia. Radioallergosorbent tests (RAST) for major food allergens were negative except egg-white. A bone marrow biopsy demonstrated an increased number of eosinophil lineage cells and no blasts. His karyotype was normal. Molecular analysis for the Fip1-like1-Platelet Derived Growth Factor Receptor, α chain fusion gene [9], was negative. Albumin was administered intravenously because he showed oligouresis and hypotension. Administration of prednisolone (PSL) was started at the same time and the patient responded very well. In addition, elemental diet was used to eliminate multiple

allergens. However, when the patient was set on a taper, he required a dose of 1 $mg \cdot kg^{-1} \cdot day^{-1}$ of prednisolone in order to eliminate the eczema with edema and hypereosinophilia. Despite the dose of PSL, frequent vomiting appeared, again and then persisted. Therefore, an upper gastrointestinal endoscopy was performed. Endoscopic findings showed erosion in gastric mucosa and edema in duodenal mucosa. A biopsy revealed increased eosinophilic infiltration with plasma cells and hyperemic edema in the lamina propria in duodenal mucosa (Figure 1A) and increased eosinophilic infiltration, interstitial edema, hyperemia and bleeding in gastric mucosa. This finding motivated us to increase the dose of PSL to 2 $mg \cdot kg^{-1} \cdot day^{-1}$. The higher dose of PSL reduced the frequency of vomiting and diminished the intestinal eosinophil infiltration, according to a reevaluation by endoscope. Although exacerbation of symptoms and hypereosinophilia were observed when tapered the steroid, despite of more than one year treatment of PSL and elemental diet, the PSL was tapered slowly and epinastine and suplatast tosilate had a steroid-sparing effect. Currently, the patient remains completely off steroids and his eosinophil count has been within normal range under these drugs.

Case 2: A 2-month-old girl who had been hospitalized with mild myocarditis that seems to be associated with viral infection, since the age of 55 days, presented mucous and bloody stool after improvement of the myocarditis. She was a mixed-fed infant and previously healthy. Although peripheral blood eosinophil count was normal range when admitted, laboratory data showed peripheral blood hypereosinophilia and detectable eosinophils in the mucous and bloody stool at that time. The relationship between the bloody stool containing eosinophils and the myocarditis remained unclear. A radiographic contrast enema was performed and presented a finding suggestive of follicular lymphoid hyperplasia. Mucous and bloody stool were the only symptoms. Hydrolyzed formula eliminated the mucous and bloody stool within several days, although spotted blood was detected for a longer time. A normal diet was resumed after confirming that the provocation test was negative. Currently, she has had neither mucous nor bloody stool.

Case 3: A 3-month-old boy was admitted to our hospital due to persistent bloody stool that had appeared a month before the visit. He was a mixed-fed infant and had good feeding and no poor weight gain. Laboratory data showed peripheral blood hypereosinophilia and detectable eosinophils in his stool. The patient was suspected to have a colon polyp and had a colonoscopy. The colonoscopy revealed mucosal edema of cecal and ascending colon and lymphoid hyperplasia of rectum and sigmoid colon. The histological findings showed eosinophil and lymhocytes infiltrations with interstitial edema, hyperemia and bleeding in the lamina propria. The eosinophils were detectable in crypts and seemed to be degranulated (Figure 1B). After switching from mixed feeding to only breast milk feeding, the bloody stool disappeared within a few days.

Case 4: A 2-month-old, mixed-fed baby girl was admitted to our hospital due to sustained bloody stools beginning at 33 days of age, although she was otherwise healthy. Her weight gain had been good despite the bloody stool. Laboratory data showed peripheral blood hypereosinophilia and positive fecal eosinophils. ALSTs of α-lactalbumin and α, β, and κ-casein were positive. A radiographic contrast enema presented a segmental narrowing with granular mucosa on a serrated wall of the colon. Colonoscopic examination demonstrated several mucosal erythemas of the colon and rectum (Figure 1D). The colonic and rectal biopsies revealed intense eosinophil

infiltrations in the crypt epithelium with Charcot-Leyden crystals (Figure 1C). In order to eliminate milk allergens from the breast milk, her mother took in a strict dairy-free diet. After dairy-free breast milk was used, the bloody stool was resolved within a month. After a confirmation of negative in the provocation test, the mother was released from the elimination of dairy in her diet. Since then, her breast milk has not induced any symptoms.

Case 5: An 8-day-old girl in whom bloody stool was detected just after her first artificial milk feeding at 1 day of age was admitted to our hospital due to exacerbation of the symptom with poor milk feeding. The patient was treated with intravenous fluid, without ingesting anything orally. The patient developed vomiting in addition to bloody stool. The next day, milk was resumed and then increased in small increments. Although her daily weight gain and general condition showed some improvement, the symptoms persisted. She was referred to the allergy and immunology department. Her laboratory data showed peripheral blood hypereosinophilia and aggregation of eosinophils in her mucous and bloody stool on consultation of allergists. A radiographic contrast enema at 17 days of age presented a lead-pipe-like stenosis of the descending and sigmoid colon (Figure 2). By 19 days of age, the symptoms had resolved. On day 27, the elimination of milk allergens was started, since her peripheral blood showed persistent hypereosinophila and positive milk-specific IgE. A follow-up radiographic contrast enema at 3 months of age revealed an improvement of the narrowing of the sigmoid colon. At 6 months, as the provocation test was negative, the patient returned to normal formula. Although she had often had mild eczema and recurrent wheeze associated with respiratory viral infection, she has had neither mucous nor bloody stool, currently.

Discussion

EGIDs are heterogeneous disorders categorized by gastrointestinal eosinophil inflammation [1]. We experienced 5 cases of EGIDs, including secondary EGIDs associated with HES (summarized in Table1). Case 1 was a secondary eosinophilic gastroenteritis with HES. The patient presented hypereosinophilia greater than >1,500 eosinophils/μl for more than 6 months (2,980-31,158 cells/μl in stable condition for a last 6 month before admission) and symptoms of organ involvements in skin and gastrointestinal tract. In addition, he also showed mild mitral and tricuspid valve regurgitation and prolapse of mitral valve in heart and stenosis of the ureteropelvic junction. However, a causal linkage between these findings and eosinophilic inflammation could not be confirmed. Elimination of multiple allergens would not be sufficient to improve the symptoms and eosinophilia. Unlike acute allergic reactions, chronic allergy is rarely associated with absolute eosinophil counts of more than >2,000 cells/μl[10]. Besides, the presence of immature granulocytic cells with hypereosinophila in peripheral blood may imply the patient had a primary hematopoietic disorder[11]. About 40 pediatric cases of hypereosinophilic syndromes have been reported, based on the literature in the English language [12]. However, infant-onset of HES is extremely rare. This patient was also associated with a congenital syndrome, BWS. However, no report shows the relationships between hematological disorders or allergic disorders and BWS [8,13]. In addition, although pediatric HES is often associated with chromosomal abnormalities [12], this patient's karyotype was normal. Interestingly, despite 1 $mg \cdot kg^{-1} \cdot day^{-1}$ of PSL, the patient presented symptomatic eosinophilic infiltration of the

intestine and a higher dose of PSL was required to resolve the symptom, suggesting that intestinal eosinophil infiltration associated with HES may be more persistent compared to that of primary EGIDs. As another interesting point, splatast tosilate and epinastine were used since anti-eosinophilic effects have been reported in these drugs [14,15]. These drugs could be effective at least for steroid-sparing in case 1.

Eosinophilic colitis (EC) shows a bimodal age distribution in infant and adolescence. the infantile EC presented at a mean age at diagnosis of approximately 60 days [1]. In infants, EC, allergic colitis (AC), and FPIP are significantly overlapping disorders sometimes approached by different points of view [6,7,16]. It seems reasonable that EC in infants is considered as a histologically proven AC or FPIP. All of cases 2–5 showed bloody stool as an initial symptom. They may be categorized food protein-induced enterocolitis syndrome (FPIES) or FPIP [4]. Interestingly, case 5 appeared to be distinguishable from the other 3. In fact, Case 5 had an earlier and severer onset of vomiting than the other 3 patients and tested positive for milk-specific IgE.

Milk-specific IgE was mostly negative in patients with allergic colitis or eosinophilic colitis, which is typically a non-IgE-mediated allergy [1,4]. Therefore, allergic eosinophilic enterocolitis was suspected in Case 5.

Concerning the diagnosis of allergy, in addition to the usual IgE-mediated diagnostic tests, ALST and the atopy patch test are useful as adjunctive diagnostic tests when a non-IgE-mediated allergy is suspected [17]. For a definitive diagnosis, the elimination and challenge of allergens are recommended [7]. As a distinctive approach, the histological findings associated with eosinophil infiltrations—for example, more than 20 eosinophils per HPF (87 and 130 eosinophils/ HPF in case3 and 4, respectively)—are also reported to be good criteria for the diagnosis of allergic colitis [6,18,19]. A cluster of eosinophils in the mucous and bloody stool may be of diagnostic value. Peripheral blood hypereosinophila could be important since the eosinophil count is often checked routinely as a differential count of leukocytes even in those patients not suspected of having allergies. EC (AC) was suspected in case 2 based on peripheral blood and stool examinations[20] after excluding surgical diseases such as colon polyps and intussusceptions. A definitive diagnosis of EC was made by the histological findings in cases 3 and 4.

Although there are a limited number of studies showing radiological findings of allergic colitis, eosinophilic colitis, or enterocolitis, detectable radiological findings are not common [21,22]. Lymphoid hyperplasia has occasionally been presented but is not always a pathological condition[17]. Surprisingly, a radiographic contrast enema revealed a narrowing of the colon in cases 4 and 5. Radiographic examination may be useful as an adjunct to the diagnosis of EC.

Based on the literature, 18% of infants with bloody stool were confirmed by an elimination and provocation test as being allergic to cow's milk [7], whereas another report showed that 64% of patients with rectal bleeding had histological findings-proven AC [6]. The great difference between these 2 groups could be interpreted as follows. First, although cow's milk is the most common cause of AC, milk-associated proteins are not the sole cause of AC, since infants become sensitized to the proteins excreted in breast milk [17]. Second, there is the possibility that the patients have already become tolerant during elimination [17]. A significant proportion of patients developed tolerance in one year of a strict elimination diet [17]. In addition, there are types of eosinophilic colitis that do not present any allergic reactions, like neonatal transient

eosinophilic colitis [23]. Indeed, the elimination and provocation tests were negative in our cases. Therefore, it seems important to carefully observe biopsy-proven AC, as well as those patients diagnosed by the elimination and provocation test, which is the gold standard for diagnosis.

Only 18% of patients with AC were allergic to cow's milk, as mentioned above [7]. In addition, AC proved to be benign and self-limiting and, in most cases, cow's milk elimination did not affect the duration of bleeding [7]. Another problem is that the elimination and provocation test for AC is available only in restricted hospitals as compared with the routinely performed provocation test. These facts may discourage pediatricians and pediatric surgeons from the further investigation of allergies, resulting in missing patients with AC.

In conclusion, intestinal eosinophil infiltration would seem to be a common finding in all the patients presented here, but the clinical findings and courses vary. To clarify the cause of gastrointestinal eosinophil infiltration, histological analysis, as well as the elimination and provocation test, would be useful.

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Figure Legends

Figure 1. **Histological and endoscopic findings of the patients**
Histopathologic analysis of the duodenum in Case 1 (A) and the colon in Case 3 (B) and Case 4 (C) was performed by hematoxylin and eosin staining (optical magnifications X 200). The arrow is pointing to a Charcot-Leyden crystal. Panel D represents the endoscopic findings in Case 4. Insets represent blow-ups of original pictures (A-C).

Figure 2. **A radiographic contrast enema examination of the patient**
A radiographic contrast enema examination was performed in Case 5. The arrow is pointing to the narrowing of the colon.

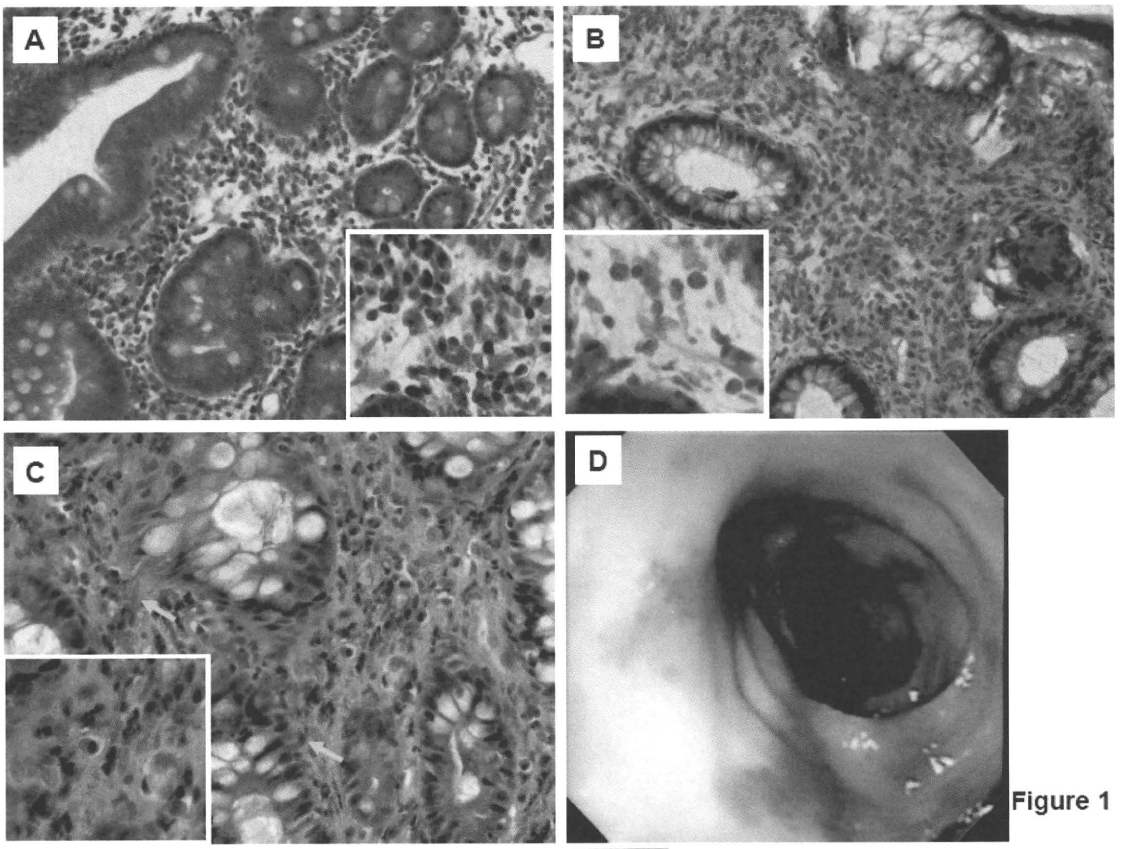

Figure 1

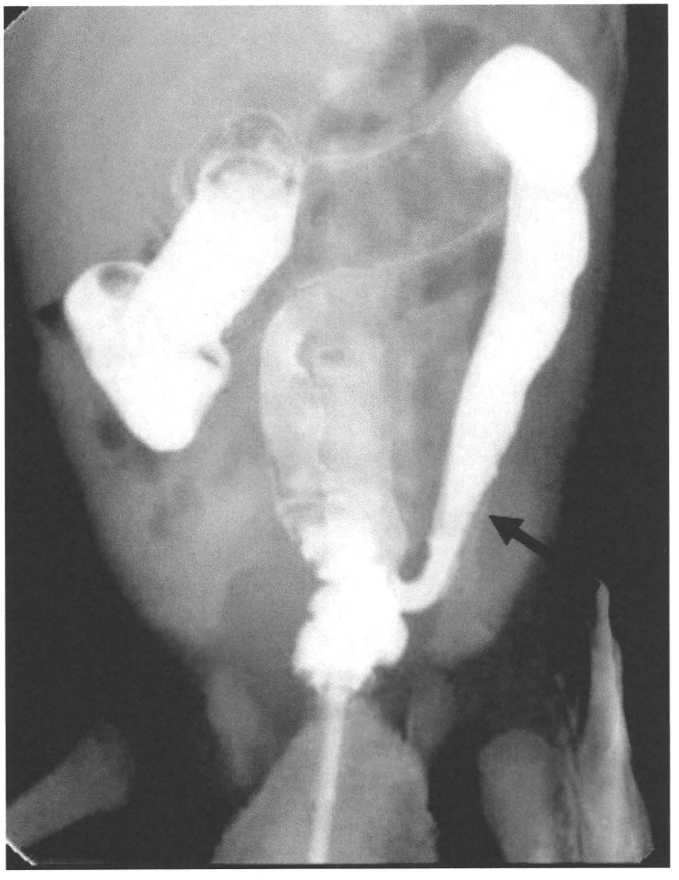

Figure 2

Table 1. Characteristics of Patients with EGIDs

Patient No.	1	2	3	4	5
Age/sex	8 months/male	2 months/female	3 months/male	2month/female	8 days/female
Chief complaint	exacerbation of eczema	Bloody stool	Bloody stool	Bloody stool	Bloody stool
Peripheral blood eosinophils (/μl)	22,410	2,136	3,052	3,154	7,375
Total IgE antibody (IU/ml)	41.5	14.5	5.09	< 2.0	12.6
Positive Specific IgE antibody	Egg-white	-	-	-	Milk
CRP (mg/dl)	0.1	0.0	0.0	0.0	0.0
Stool examination	nd	Eos (+)	Eos (+)	Eos (+)	Eos (+)
ALST	nd	nd	nd	+	nd
Barium Enema	nd	LH	LH	stenosis of colon	stenosis of colon
Endoscopy	Edema in duodenum	nd	LH and edema in colon	Edema and erythema in colon	nd
Histology	Eos with PC	nd	LH and Eos with Ly	Eos with CLC in crypt Epi	nd
Provocation test*	nd	- /1.2y	nd	- /5M	- /7M
Treatment	Prednisolone	Elimination	Breast milk alone	Elimination	Elimination
Diagnosis**	EGE/HES	EC	EC	EC	AEEC

nd, not done; M, months; Y, year; ALST, allergen-lymphocyte stimulation test; Eos, eosinophils; Ly, lymphocytes; PC, plasma cells; Epi, epithelium; CLC, Charcot-Leyden crystal ; LH, lymphoid hyperplasia; AEEC, Allergic eosinophilic enterocolitis; EC, Eosinophilic colitis; EGE, Eosinophilic gastro enteritis; HES, Hypereosinophilic syndrome; Elimination, Elimination of cow's milk allergens

*result of test/ the age when performed provocation test
**including suspected cases

Review

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FIP1L1/PDGFRα-Associated Systemic Mastocytosis

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Key Words
Chronic eosinophilic leukemia · Eosinophils · FIP1L1/PDGFRα · Hypereosinophilic syndromes · Interleukin-5 · Mast cells · Stem cell factor · Systemic mastocytosis

Abstract
Since the identification of the *FIP1L1/PDGFRA* fusion gene as a pathogenic cause of the hypereosinophilic syndrome (HES), the importance of the molecular classification of HES leading to the diagnosis of chronic eosinophilic leukemia (CEL) has been recognized. As a result, a new category, 'myeloid and lymphoid neoplasm with eosinophilia and abnormalities in PDGFRA, PDGFRB or FGFR1', has recently been added to the new WHO criteria for myeloid neoplasms. FIP1L1/PDGFRα-positive disorders are characterized by clonal hypereosinophilia, multiple organ dysfunctions due to eosinophil infiltration, systemic mastocytosis (SM) and a dramatic response to treatment with imatinib mesylate. A murine HES/CEL model by the introduction of FIP1L1/PDGFRα and IL-5 overexpression also shows SM, representing patients with FIP1L1/PDGFRα-positive HES/CEL/SM. The murine model and the in vitro development system of FIP1L1/PDGFRα-positive mast cells revealed the interaction between FIP1L1/PDGFRα, IL-5 and stem cell factor in the development of HES/CEL/SM. Current findings of FIP1L1/PDGFRα-positive HES/CEL are reviewed focusing on aberrant mast cell development leading to SM.

Introduction

The importance of the molecular classification of the hypereosinophilic syndrome (HES) has been increasingly recognized. The fusion gene *FIP1L1/PDGFRA* was identified in a large number of patients initially diagnosed as having a myeloproliferative variant of HES or chronic eosinophilic leukemia (CEL) [1]. Subsequently, other variant PDGFRA fusion genes as well as those involving PDGFRB or FGFR1 have also been described in myeloproliferative neoplasms with eosinophilia in the last years [2–4]. As a result, a new category of myeloid neoplasms, 'myeloid and lymphoid neoplasm with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1', has recently been added to the new WHO criteria [5]. FIP1L1/PDGFRα fusion-positive disorders are characterized by clonal myeloproliferation resulting in hypereosinophilia, multiple organ dysfunctions due to eosinophil infiltration, a dramatic response to treatment with

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imatinib mesylate and systemic mastocytosis (SM) [6]. Murine models of FIP1L1/PDGFRα-induced diseases have been reported recently [7, 8]. Interestingly, these models demonstrated severe SM representing patients with FIP1L1/PDGFRα fusion-positive diseases [9]. In this review, the clinical manifestation of FIP1L1/PDGFRα fusion-associated disorders are summarized, focusing on mastocytosis induced by FIP1L1/PDGFRα expression, and the mechanisms of mastocytosis in FIP1L1/PDGFRα-positive HES/CEL are discussed.

Eosinophilia in SM Patients

Peripheral blood eosinophilia has been reported in 15–28% of SM patients [10–12]. This is no big surprise since crosstalk between eosinophils and mast cells is well known, especially in allergic inflammation. For instance, mast cell activation by major basic protein, an eosinophil granule protein, elicits the generation of lipid mediators and cytokines. Eosinophils also produce cytokines associated with mast cell activation such as stem cell factor (SCF), granulocyte/macrophage colony-stimulating factor and nerve growth factor [13]. The D816V mutation in the *KIT* gene resulting in constitutive activation of the receptor tyrosine kinase has been shown in the majority of patients as a cause of SM [14]. D816V-kit mutation-positive SM with eosinophilia has been clinically distinguished from that without eosinophilia. D816V-kit mutation-positive SM patients with eosinophilia present hepatosplenomegaly, lymphadenopathy, anemia and monocytosis more frequently as well as higher levels of circulating tryptase, whereas anaphylaxis is seen with a low frequency in these patients, in comparison to patients without eosinophilia [10].

Clinical Manifestations of Mastocytosis Associated with FIP1L1/PDGFRα

A recent report has shown that FIP1L1/PDGFRα-associated SM is a clinically distinguishable disease from D816V mutation SM with eosinophilia [10]. FIP1L1/PDGFRα-associated SM shows lower tryptase levels in the circulation, less aggregation of bone marrow mast cells, more severe eosinophilia, higher serum vitamin B12 levels and more frequent pulmonary and cardiac involvement than D816V SM with associated eosinophilia. The clinical difference is important since it would justify the differential diagnosis between these two entities, based on the analysis of the expression of the FIP1L1/*PDGFRA* fusion gene. More recently, Klion [15] proposed a scoring system to approach FIP1L1/PDGFRα fusion-positive HES/CEL therapy appropriately.

SM in Murine Models of FIP1L1/PDGFRα-Positive Disorders

First, Cools et al. [7] reported that the introduction of the *FIP1L1/PDGFRA* fusion gene into bone marrow hematopoietic stem cells and progenitors (HSC/P) induces a murine model of a myeloproliferative disorder (MPD) similar to that found in p210-BCR/ABL-induced chronic myelogenous leukemia-like disease (F/P-MPD). Subsequently, an HES/CEL murine model was developed by the introduction of the *FIP1L1/PDGFRA* fusion gene into bone marrow HSC/Ps in the presence of T-cell overexpression of IL-5 (F/P-HES/CEL) [8]. More recently, these two murine models were also shown to develop tissue mast cell infiltration and increased circulating mast cell protease 1 (MMCP-1) levels, which is a systemic assay of mast cell content and degranulation in the mouse resembling serum tryptase determination in SM patients [9]. Similar to the patients with *FIP1L1/PDGFRA* fusion gene, tissue mast cell infiltration of hematopoietic organs, skin and intestine, where mast cell morphology is aberrant, is present in F/P-HES/CEL mice. Tissue mast cell shape is irregular with frequent cytoplasmic extensions reminiscent of the 'spindle shape' found in clinical SM. In addition, serum levels of MMCP-1 are extremely elevated in F/P-HES/CEL mice.

A possible interaction of IL-5 with the SM phenotype was analyzed in F/P-HES/CEL mice. F/P-HES/CEL and F/P-MPD mice showed significantly greater mast cell infiltration in their skin and intestine, and higher levels of MMCP-1 compared to both controls with and without IL-5 overexpression. Interestingly, intestinal mast cell infiltration and serum MMCP-1 levels in F/P-HES/CEL mice were significantly higher compared to F/P-MPD, suggesting that FIP1L1/PDGFRα in conjunction with IL-5 exacerbates mastocytosis in murine F/P-HES/CEL [9].

Mechanism of FIP1L1/PDGFRα-Promoted Mast Cell Development

Since the c-kit signaling pathway is pivotal for normal mast cell development and function, the question of whether FIP1L1/PDGFRα-associated SM is still c-kit de-