Eosinophilic Fasciitis: A Single Center Experience of Seven Patients

Oded Shamriz MD[1], Mariana Druker Bsc[2], Tzahi Neuman MD MHA[3], Zvi Dranitzki MD[2] and Yuval Tal MD PhD[2]

[1]Pediatric Division and [2]Clinical Immunology and Allergy Unit, Internal Medicine Division, and [3]Pathology, Hadassah–Hebrew University Medical Center, Ein Kerem Campus, Jerusalem, Israel

ABSTRACT: **Background:** Eosinophilic fasciitis (EF) is a rare disease characterized by scleroderma-like skin, inflammation of deep muscle fascia, hypergammaglobulinemia, peripheral eosinophilia, and elevated erythrocyte sedimentation rate.

Objectives: To present our experience in diagnosis and treatment of seven biopsy-proven EF patients in a large tertiary medical center.

Methods: We screened all patients who were admitted to our tertiary medical center and diagnosed with EF by tissue biopsies from January 2000 to January 2016. We analyzed relevant patient files regarding diagnosis, treatment, and outcome parameters. A comprehensive framework was presented based on the results of our observations and the corresponding literature.

Results: We identified seven patients (six males; one child). Mean age at diagnosis was 37.4 years (range 10–67 years). Underlying autoimmune disorders were observed in three patients (42.8 %). Disease anatomical distribution was noted in lower and upper limbs (85.7% and 57.1%, respectively) as well as neck and shoulders (14.3% each). Three patients (42.8%) had a history of initial misdiagnosis. The mean time period from first clinical presentation to histopathological diagnosis was 150.3 days (range 16–602 days). Treatment included oral glucocorticoids (71.4%), pulse methylprednisolone (14.2%), and methotrexate (42.8%). Recovery from symptoms related to EF was observed in six patients.

Conclusions: Diagnosis of EF is primarily based on clinical and histopathological findings. As eradication of this disease can be expedited with early treatment, it is important to increase awareness in the medical community.

IMAJ 2018; 20: 95–99

KEY WORDS: eosinophilic fasciitis, Shulman syndrome, eosinophilia, eosinophilic disorders, autoimmunity

Eosinophilic fasciitis (EF), also known as Shulman syndrome, is a disease characterized by scleroderma-like skin, inflammation of deep muscle fascia, and peripheral eosinophilia [1]. The disease is rare, with just over 300 reported cases worldwide [2]. Clinical presentation includes weight loss (26% of patients), myalgia with or without stimulation (67%), and weakness (38%) [3]. Cutaneous manifestations include peripheral edema, skin induration, morphea, skin appearance of peau d'orange, groove sign, contractures, and hyperpigmentation [1].

Etiology is unknown. Several conditions were found to be associated with EF, including solid and hematological malignancies, infections (mainly borreliosis), autoimmune diseases, and medications [1]. Strenuous exercise or trauma were described in 46% of cases [3].

Laboratory evaluation in these patients is characterized by increased inflammation indices, including elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and hypergammaglobulinemia [3]. Peripheral eosinophilia is observed in 63–93% of patients [1]. Anti-nuclear antibodies (ANA) and high creatine phosphokinase (CPK) are rarely elevated [1]. Aldolase-1 levels are elevated and can be used as a marker for the disease [4]. Imaging of choice is magnetic resonance imaging (MRI), which demonstrates thickening of the fascia tissue surrounding the muscles and subcutaneous edema [5,6]. A definitive diagnosis can be achieved by a muscle biopsy [1].

The treatment of choice is glucocorticosteroids [1,7]. However, other immunosuppressive drugs including methotrexate, azathioprine, penicillamine, and tacrolimus, were also used [8,9].

In this study, we describe seven biopsy-proven EF patients admitted to our medical center. We characterize clinical parameters, laboratory and histopathological diagnoses, and treatment modalities, as well as clinical outcome.

PATIENTS AND METHODS

STUDY DESIGN

We conducted a retrospective search through the medical records for patients of all ages admitted to our tertiary medical center (Hadassah-Hebrew University Medical Center, Ein Kerem Campus, Jerusalem, Israel) and diagnosed with EF by tissue biopsies from January 2000 to January 2016. For the computerized search we used the following keywords, according to the international classification of diseases (ICD)-9 coding (728.89): "other disorders of muscle, fascia and ligament" and "eosinophilic fasciitis." Data regarding hospitalization, diagnosis (clinical, laboratory, and histopathological), treatment, and outcome were collected.

PATIENTS

Patient baseline characteristics are presented in Table 1. In the time period of the study, a total of 327 patients were admitted with the general diagnosis of "other disorders of muscle, fascia and ligament." Of these patients, three were identified and diagnosed with a biopsy-proven EF. An additional six patients who did not appear in the computerized search were added from the records of pathology department. Of these patients, two were excluded due to insufficient data available. A total of seven patients (six males; one child) were included in the study. Jewish ethnicity was noted in six patients (85.7%). Mean age at diagnosis was 37.4 years (range 10–67 years).

ETHICS REVIEW OF THE STUDY

The study was approved by an institutional ethics committee at our medical center.

RESULTS

CLINICAL MANIFESTATIONS

Clinical manifestations are presented in Table 1. Underlying immune system-related disorders were observed in three patients (42.8 %). These included common variable immune deficiency and immune thrombocytopenia purpura (ITP; patient 1); Sjögren's syndrome, celiac disease, and ulcerative colitis (patient 2); and Hashimoto's thyroiditis (patient 6). Disease anatomical distribution was noted in lower limbs of six patients (85.7%), upper limbs in four patients (57.1%), one patient each in neck and shoulders (14.3%). Disease features included lower limb edema in five patients (71.4%), myalgia in five patients (71.4%), arthralgia in three patients (42.8%), and fatigue and peau d'orange in one patient each (14.3%). Raynaud phenomenon, morphea, joint contracture, and visceral involvement were not observed in any of the patients. Muscle weakness was noted in most patients. Pain or swelling of the involved muscle was noted on physical examination in three patients (42.8%).

LABORATORY AND HISTOPATHOLOGICAL DIAGNOSIS

Data regarding diagnosis, treatment, and patient outcome is presented in Table 2. Laboratory workup included peripheral blood eosinophilia in four patients (average 1158; normal range 40–400 cells × 10^6/L). Borderline positive ANA titer was observed in two patients (patients 5 and 6). In these two patients, hypergammaglobulinemia was also noted. However,

Table 1. Clinical and baseline characteristics

Patient	Age at diagnosis (years)	Gender	Ethnicity	Underlying conditions	Underlying autoimmune disorders	Disease distribution	Lower limb edema	Peau d'orange	Fatigue	Arthralgia	Myalgia
1	31	Female	Jewish	Hypothyroidism, ITP, CVID	+	Lower and upper limbs	+	-	-	-	+
2	47	Male	Jewish	UC, Sjögren's syndrome, CD, HP PUD	+	Neck	-	-	-	-	-
3	34	Male	Jewish	-	-	Lower and upper limbs	+	+	-	-	+
4	10	Male	Arab	Tonsillectomy due to recurrent tonsillitis	-	Lower limbs	-	-	-	-	+
5	29	Male	Jewish	-	-	Lower and upper limbs	+	-	-	+	+
6	44	Male	Jewish	Hashimoto's thyroiditis	+	Lower limbs, shoulders	+	-	-	+	-
7	67	Male	Jewish	Nephrolithiasis, hiatal and diaphragmatic hernias, primary hyper-parathyroidism	-	Lower and upper limbs	+	-	+	+	+

ITP = immune thrombocytopenic purpura, CVID = common variable immune deficiency, UC = ulcerative colitis, CD = celiac disease, HP = *Helicobacter pylori*, PUD = peptic ulcer disease

Table 2. Diagnosis, treatment, and patient outcome

Patient*	Time period from clinical presentation to diagnosis (days)	History of misdiagnosis	ESR (1–20 mm/h)	CRP (0–0.5 mg/dl)	CPK (40-200 IU/L)	Absolute eosinophils count (40–400 cells × 10^6/L)	MTX	Pulse methylpred-nisolone	Oral GCS	Follow-up period (years)	Outcome
1	602	Septal panniculitis	12	3.3	65	100	-	-	+	1.71	CR
2	NA	-	NA	81	NA	NA	+	-	+	4.45	CR
3	21	-	5	4.9	25	2700	+	+	+	1.27	CR
4	97	Metabolic disorder**	NA	NA	58,141	NA	-	-	-	0.27	symptomatic, lost to further follow-up
5	91	-	46	7	29	900	+	-	+	5.97	CR
6	16	Fibromyalgia	45	4.59	< 20	1290	-	-	-	1.16	CR
7	75	-	NA	1.1	79	800	-	-	+	4.04	CR

NA = data is not available, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, CPK = creatine phosphokinase, ANA = anti-nuclear antibody titer, MTX = methotrexate, GCS = glucocorticosteroids, CR = complete resolution of eosinophilic fasciitis symptoms

*All patients were diagnosed by muscle biopsies

**Initial differential diagnosis included rhabdomyolysis, mitochondrial disease, very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, and central core disease

data regarding immunoglobulin levels was not available in three patients (patient 1, 2, and 4). Average CRP and ESR were 16.98 mg/dl (normal range 0–0.5 mg/dl) and 27 mm/h (normal 1–20 mm/h), respectively. CPK was increased in patient 4.

Histopathological features of the patients in our study included edema and infiltration of lymphocytes, histiocytes, plasma cells, and eosinophils into deep fascia. Furthermore, marked thickening of the deep fascia and fibrosis were observed. Representative histopathological slides of two patients (patients 1 and 6) are presented in Figure 1.

None of the selected patients in our study had had a MRI. In three patients (42.8%) medical records noted a history of initial misdiagnosis [Table 1]. Mean time period from first clinical presentation to histopathological diagnosis was 150.3 days (range 16–602 days).

TREATMENT MODALITIES AND OUTCOME

Treatment and outcome are presented in Table 2. Five patients (71.4%) were treated with oral glucocorticosteroids. Pulse methylprednisolone was given to only one patient (14.3%). Three patients (42.8%) were treated with methotrexate. One patient received non-steroidal anti-inflammatory drugs. Patient 4 was lost to follow-up after diagnosis and before starting treatment. Patient 6 refused medical treatment. Surgical intervention was not noted in any of the patients. Mean follow-up period was 2.7 years (range 0.27–5.97 years). Complete resolution of symptoms related to EF was noted in six patients.

DISCUSSION

In this report, we describe our experience in the diagnosis and treatment of seven biopsy-proven EF patients.

The mean age at diagnosis was 37.4 years, which corresponds well with previous EF reports with a mean age of 40–50 years [1,10]. In our study, EF predominantly affected young men (85.7% males). However, in other reports concerning EF, female predominance was observed [10,11].

In most of our cases (85.7%), involvement of lower or upper limbs was noted. Previous reports described clinical presentation of lower and upper limbs in 88% and 70% of the patients, respectively [3]. Anatomical distribution was also reported to include back and chest (17–32%) and neck (6–18%) [1,3]. This finding was also seen in our series, as patient 2 presented with a neck-limited disease. Truncal involvement was not observed in any of our patients, and neither was respiratory restrictive disease.

Three patients in our cohort had underlying autoimmune diseases. Association of EF with autoimmune diseases such as autoimmune hemolytic anemia, Hashimoto's thyroiditis, and ITP were previously described [12,13]. Overlap syndromes of EF with other autoimmune diseases such as systemic sclerosis (SSc), mixed connective tissue disease, and vasculitis have also been reported [14-17]. However, in more than 75% of EF cases, ANA titers are not elevated and other autoantibodies, such as anti-dsDNA, are usually negative [1]. Therefore, the exact role of autoimmunity in EF pathogenesis remains unclear.

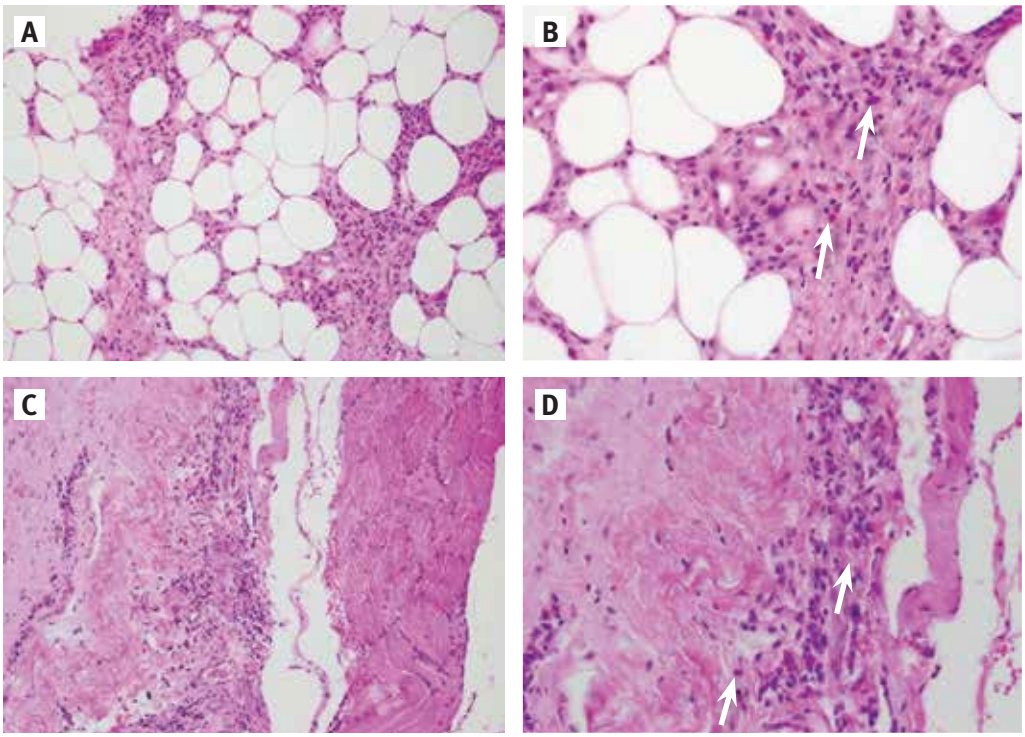

Figure 1. Two representative cases compatible with eosinophilic fasciitis. **[A-B]** Histopathological sections from the thigh of patient 1 and **[C-D]** arm of patient 6 showing edema and an infiltration of lymphocytes, histiocytes, plasma cells, and eosinophils. Eosinophils (white arrows) are in only focal collections **[A-B, C-D]**. There is striking thickening of the deep fascia **[C-D]** and septa **[A-B]** of the subcutis with fibrosis, fibrin deposition and hyalinization of the collagen. Hematoxylin & Eosin stains: magnification ×100 **[A, C]** and magnification ×200 **[B, D]**

Diagnosis of EF is challenging. Clinical signs and symptoms, as well as exclusion of other diseases, such as SSc, are crucial [1]. Differentiation of SSc from EF may be achieved by identifying "red flags," such as Raynaud's phenomenon, high titers of ANA and puffy fingers, which can be found in early stages of SSc [18]. The use of the American College of Rheumatology/European League Against Rheumatism 2013 classification criteria is also helpful, and a score ≥ 9 is diagnostic of SSc [18,19]. Moreover, Histopathological features in EF include an unaffected dermis, in contrast to tissue characteristics in SSc [11].

Other histopathological characteristics of EF consist of fascia inflammation of lymphocytes, macrophages, plasma cells, and eosinophils [1]. Cytotoxic cellular response is suspected due to a CD8+ predominant lymphocytic immuno-profile [20]. Deep fascia thickening and fibrosis may result from eosinophilic degranulation [20].

Pinal-Fernandez et al. [1] proposed major and minor diagnostic criteria for EF. These criteria enable diagnosis of EF without the need for tissue biopsy. However, currently, no such criteria are widely accepted or routinely followed by physicians. To overcome this obstacle, we included only patients with histopathological and clinical features of EF, thus ensuring a definitive diagnosis.

Initial misdiagnosis in three patients and a mean period of 150.3 days from clinical presentation to biopsy-proven EF diagnosis may account for the poor awareness by physicians to this uncommon disease. In a recently published multicenter 63-patient cohort, the time period from disease onset to EF diagnosis was reported to be 11 months [7]. Moreover, 79% of EF patients in this cohort were initially misdiagnosed. These misdiagnoses resulted in unnecessary procedures and treatments, such as bone marrow biopsies (4 patients) and chemotherapy (1 patient), These patients had been misdiagnosed with hypereosinophilic syndrome or eosinophilic leukemia [7].

Five patients in our study received treatment with oral glucocorticosteroids and in three, methotrexate was added. Glucocorticosteroids are still considered first-line therapy, whereas pulse intravenous methylprednisolone therapy was found to be associated with a favorable outcome [1,21]. However, the combination of glucocorticosteroids, either by oral or intravenous pulse therapy, and methotrexate was found to be safe and to increase rates of complete remission [7,22]. In refractory cases, successful treatments with sirolimus and tocilizumab were also described [23,24].

In our study, complete resolution of EF symptoms is seen in six patients. Young age at disease onset, clinical presentation (morphea or trunk involvement), and diagnosis time delay of over 6 months, were previously reported to be associated with poor outcome [20,21]. Patient 6 refused treatment, yet had spontaneous remission. EF might be self-limited in a selective number of patients [1]. Complete and partial recovery were seen in 1% and 2%, respectively, of patients who did not receive glucocorticosteroids therapy [7]. However, no clinical or laboratory predictors are currently known for a self-limited disease course.

Our study has important limitations. It is a small, retrospective medical record analysis. Due to its nature, drawing conclusions about disease course and proper management is problematic. However, since EF is rare, most cohorts published so far are small in size [7,10,11,13,25]. Therefore, we think our report contributes to the existing literature.

CONCLUSIONS

Diagnosis of EF is based on clinical and histopathological findings. As eradication of this disease can be expedited with early treatment, it is vital that we work to increase awareness of this malady among the medical community.

Correspondence
Dr. Y. Tal
Clinical Immunology and Allergy Unit, Internal Medicine Division, Hadassah–Hebrew University Medical Center, Ein Kerem, Jerusalem 9112001, Israel
email: yuvaltal@hadassah.org.il

References

1. Pinal-Fernandez I, Selva-O' Callaghan A, Grau JM. Diagnosis and classification of eosinophilic fasciitis. *Autoimmun Rev* 2014; 13: 379-82.
2. Das J, Chinoy H, Dick J, Matthews R, Roberts M. A literature review of eosinophilic fasciitis with an illustratrative case. *Curr Rheumatol Rev* 2017; 13 (2): 113-20.
3. Lebeaux D, Sene D. Eosinophilic fasciitis (Shulman disease). *Best Pract Res Clin Rheumatol* 2012; 26: 449-58.
4. Nashel J, Steen V. The use of an elevated aldolase in diagnosing and managing eosinophilic fasciitis. *Clin Rheumatol* 2015; 34: 1481-4.
5. Sugimoto T, Nitta N, Kashiwagi A. Usefulness of magnetic resonance imaging in eosinophilic fasciitis. *Rheumatol Int* 2007; 27: 791-2.
6. Desvignes-Engelbert A, Sauliere N, Loeuille D, Blum A, Chary-Valckenaere I. From diagnosis to remission: place of MRI in eosinophilic fasciitis. *Clin Rheumatol* 2010; 29: 1461-4.
7. Wright NA, Mazori DR, Patel M, Merola JF, Femia AN, Vleugels RA. Epidemiology and treatment of eosinophilic fasciitis: an analysis of 63 patients from 3 tertiary care centers. *JAMA Dermatol* 2016; 152: 97-9.
8. Mendoza FA, Bai R, Kebede AG, Jimenez SA. Severe eosinophilic fasciitis: comparison of treatment with D-penicillamine plus corticosteroids vs. corticosteroids alone. *Scand J Rheumatol* 2016; 45: 129-34.
9. Berianu F, Cohen MD, Abril A, Ginsburg WW. Eosinophilic fasciitis: clinical characteristics and response to methotrexate. *Int J Rheum Dis* 2015; 18: 91-8.
10. Bischoff L, Derk CT. Eosinophilic fasciitis: demographics, disease pattern and response to treatment: report of 12 cases and review of the literature. *Int J Dermatol* 2008; 47: 29-35.
11. Antic M, Lautenschlager S, Itin PH. Eosinophilic fasciitis 30 years after - what do we really know? Report of 11 patients and review of the literature. *Dermatology* 2006; 213: 93-101.
12. Bachmeyer C, Monge M, Dhote R, Sanguina M, Aractingi S, Mougeot-Martin M. Eosinophilic fasciitis following idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia and Hashimoto's disease. *Dermatology* 1999; 199: 282.
13. Minciullo PL, Morabito F, Mandaglio R, Iacopino P, Gangemi S. Eosinophilic fasciitis associated with autoimmune phenomena after bone marrow transplantation: report of two cases. *Clin Rheumatol* 2006; 25: 80-2.
14. Kivity S, Katz M, Langevitz P, Eshed I, Olchovski D, Barzilai A. Autoimmune syndrome induced by adjuvants (ASIA) in the Middle East: morphea following silicone implantation. *Lupus* 2012; 21: 136-9.

15. Alonso-Castro L, de las Heras E, Moreno C, et al. Eosinophilic fasciitis/generalized morphea overlap successfully treated with azathioprine. *Int J Dermatol* 2014; 53: 1386-8.

16. Magaro M, Altomonte L, Zoli A, Mirone L, Massi G, Federico F. Eosinophilic fasciitis associated with inflammatory neutrophilic vasculitis. *Br J Rheumatol* 1990; 29: 145-6.

17. Maddison PJ. Mixed connective tissue disease, overlap syndromes, and eosinophilic fasciitis. *Ann Rheum Dis* 1991; 50 (Suppl 4): 887-93.

18. Guiducci S, Bellando-Randone S, Matucci-Cerinic M. A new way of thinking about systemic sclerosis: the opportunity for a very early diagnosis. *IMAJ* 2016; 18: 141-3.

19. Van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2013; 72: 1747-55.

20. Long H, Zhang G, Wang L, Lu Q. Eosinophilic skin diseases: a comprehensive review. *Clin Rev Allergy Immunol* 2016; 50: 189-213.

21. Lebeaux D, Frances C, Barete S, et al. Eosinophilic fasciitis (Shulman disease): new insights into the therapeutic management from a series of 34 patients. *Rheumatology (Oxford)* 2012; 51: 557-61.

22. Mertens JS, Zweers MC, Kievit W, et al. High-dose intravenous pulse methotrexate in patients with eosinophilic fasciitis. *JAMA Dermatol* 2016; 152 (11): 1262-5.

23. Oza VS, Walsh R, North J, Berger TG, Murase JE. Treatment of eosinophilic fasciitis with sirolimus. *JAMA Dermatol* 2016; 152: 488-90.

24. Espinoza F, Jorgensen C, Pers YM. Efficacy of tocilizumab in the treatment of eosinophilic fasciitis: report of one case. *Joint Bone Spine* 2015; 82: 460-1.

25. De Masson A, Bouaziz JD, Peffault de Latour R, et al. Severe aplastic anemia associated with eosinophilic fasciitis: report of 4 cases and review of the literature. *Medicine (Baltimore)* 2013; 92: 69-81.

Capsule

Amyloid-β plaques enhance Alzheimer's brain tau-seeded pathologies by facilitating neuritic plaque tau aggregation

Alzheimer's disease (AD) is characterized by extracellular amyloid-β (Aβ) plaques and intracellular tau inclusions. However, the exact mechanistic link between these two AD lesions remains enigmatic. Through injection of human AD-brain-derived pathological tau (AD-tau) into Aβ plaque-bearing mouse models that do not overexpress tau, **He** et al. recapitulated the formation of three major types of AD-relevant tau pathologies: tau aggregates in dystrophic neurites surrounding Aβ plaques (NP tau), AD-like neurofibrillary tangles (NFTs), and neuropil threads (NTs). These distinct tau pathologies have different temporal onsets and functional consequences on neural activity and behavior. Notably, the authors found that Aβ plaques created a unique environment that facilitated the rapid amplification of proteopathic AD-tau seeds into large tau aggregates, initially appearing as NP tau, which was followed by the formation and spread of NFTs and NTs, likely through secondary seeding events. This study provides insights into a new multistep mechanism underlying Aβ plaque-associated tau pathogenesis.

Nature Med 2018; 24: 29

Eitan Israeli

Capsule

Vaccine-derived poliovirus surveillance in China from 2001–2013: the potential challenge for maintaining polio free status

The goal of polio eradication is complete elimination and containment of all wild, vaccine-related and Sabin polioviruses. Vaccine-derived poliovirus (VDPV) surveillance in China from 2001–2013 is summarized in this report by **Wang** et al., which has important implications for the global polio eradication initiative. Acute flaccid paralysis (AFP) cases and their contacts with VDPV isolated from fecal specimens were identified in an AFP surveillance system or by field investigation. Epidemiological and laboratory information for these children were analyzed and the reasons for the VDPV outbreak was explored. VDPV was isolated from a total of 49 children in more than two-thirds of Chinese provinces from 2001–2013, including 15 VDPV cases, 15 non-polio AFP cases, and 19 contacts with AFP cases or healthy subjects. A total of three circulating VDPVs (cVDPVs) outbreaks were reported in China, resulting in six cVDPVs cases of children who had not been vaccinated with oral attenuated poliomyelitis vaccine. Among the four immunodeficiency-associated VDPVs (iVDPVs) cases, the longest duration of virus excretion was about 20 months. In addition, one imported VDPV case from Myanmar was detected in the Yunnan Province. The authors concluded that until all wild, vaccine-related, and Sabin polioviruses are eradicated in the world, high quality routine immunization and sensitive AFP surveillance should be maintained, focusing efforts on underserved populations in high risk areas.

BMC Infect Dis 2017 17 (1):742

Eitan Israeli

"Decide whether or not the goal is worth the risks involved. If it is, stop worrying"

Amelia Earhart, (1897–1937), American aviation pioneer and author, the first female aviator to fly solo across the Atlantic Ocean