Brief Report

Paraneoplastic Autoimmune Multiorgan Syndrome: A Retrospective Study from a Tertiary Care Center in South India

Abstract

Background: Paraneoplastic autoimmune multiorgan syndrome (PAMS), first described as paraneoplastic pemphigus (PNP) is a heterogeneous autoimmune syndrome with a diverse spectrum of clinical and immunopathological features associated with an internal neoplasm. **Materials and Methods:** The details of the patients diagnosed with PAMS/PNP from an Indian tertiary center between January 2010 to December 2019 were retrieved from the hospital database. The clinical manifestations, histopathological features, immunofluorescence findings, and other relevant clinical details were obtained. **Results:** There were eight patients (4 males, 4 females) with PAMS, age ranging from 8 to 46 years (mean 31 years), of whom two were 8-year-old children. The mucocutaneous manifestations were polymorphic and all had recalcitrant oral mucosal involvement. The most common mucosal presentation was pemphigus-like (5/8), and the cutaneous presentation was lichen planus-like (5/8). Castleman's disease (5/8) was the commonest neoplasm followed by thymoma (2/8). Interface dermatitis was seen in all biopsies and three different patterns of direct immunofluorescence were seen, which were intercellular "fish-net" fluorescence in the epidermis (2/8), granular/linear deposition along the basement membrane (4/8) and a combination of both patterns (1/8). Indirect immunofluorescence done on rat bladder in 3 patients showed intercellular "fish-net" fluorescence. Desmoglein levels were not elevated in any of our patients. The follow-up period ranged from 1 to 112.5 months (mean, 23.6 months) with a mortality rate of 12.5%. **Conclusion:** In our study, Castleman's disease was the most common associated malignancy, and the mucocutaneous and histopathological findings were heterogeneous. Timely diagnosis and early intervention improved the outcome in our patients.

Keywords: *Bronchiolitis obliterans, Castleman's disease, Paraneoplastic autoimmune multiorgan syndrome (PAMS), Paraneoplastic pemphigus (PNP), thymoma*

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Introduction

Paraneoplastic pemphigus (PNP), first described by Anhalt *et al*.,[1] is a rare, potentially fatal, mucocutaneous disease occurring in the presence of an underlying malignancy, particularly lymphoproliferative neoplasms.[2] It was later termed paraneoplastic autoimmune multiorgan syndrome (PAMS) since the target antigens and pathological damage are seen in multiple organs. Both humoral and cell-mediated immunity are involved,[3] and anti-plakin antibodies are mainly implicated in the pathogenesis.[4]

PAMS is mainly seen between 45 and 70 years of age and is characterized by intractable mucositis and polymorphic skin eruption. The skin manifestations can mimic pemphigus vulgaris (PV), bullous pemphigoid, erythema multiforme, lichen planus (LP), and graft-versus-host disease.[5] As the histological findings are heterogeneous, immunofluorescence and serology findings aid in diagnosis. Except for anecdotal case reports,[6-8] there are no existing studies on PAMS from India and we illustrate the characteristics of PAMS among Indian patients in this study.

Materials and Methods

The details of patients diagnosed with PAMS/PNP at a tertiary care hospital, from January 2010 to December 2019 were retrieved from the hospital database after Institutional review board approval (IRB No: 13190). The clinical manifestations, laboratory investigations, imaging findings, histopathological features, direct immunofluorescence (DIF), indirect immunofluorescence (IIF), and other

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relevant clinical information were retrieved. Desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3) levels were done for all patients.

Results

Patient characteristics

There were 8 patients with PAMS fulfilling the clinical, histopathologic and immunologic criteria as proposed by Czernik *et al*.[5] [Table 1]. The mean age at presentation was 31 years (range, 8-46 years) with equal sex distribution. The development of mucocutaneous lesions was 6 months – 1 year prior to the diagnosis of the underlying neoplasm in 5 patients, and 3 presented within 4-9 months after diagnosis of the neoplasm.

Mucocutaneous manifestations

The mucocutaneous manifestations were polymorphic and all had recalcitrant oral mucosal lesions [Table 2]. Six patients (75%) had both skin and mucosal lesions, while two (25%) had only mucosal involvement. The most common mucosal presentation was pemphigus-like (5/8), with crusted erosions and ulceration, of whom 3 had hemorrhagic crusting [Figure 1a]. It was followed by LP-like mucosal presentation (3/8) with violaceous hyperpigmentation. Vermilion border was involved in 6 patients. Among the 6 patients with skin involvement, 4 had LP-like lesions with pemphigus-like oral involvement, 1 had LP-like mucocutaneous involvement, and 1 mimicked PV. Case 2 with Castleman's disease (CD) had generalized, erythematous papular rash [Figure 1b and c] which worsened following biopsy of the mass.

Associated malignancy

Five patients had associated systemic symptoms such as high-grade fever (2/8), significant loss of weight or appetite (3/8) suggesting underlying malignancy. The most common associated neoplasm in our patients was CD, hyaline vascular variant (5/8, 62.5%), followed by thymoma (2/8, 25%), and NHL (1/8, 12.5%) and non-Hodgkin lymphoma (NHL) (1/8, 12.5%).

Investigations

Histopathological examination (HPE) done in 6/8 patients showed diverse patterns: (a) interface

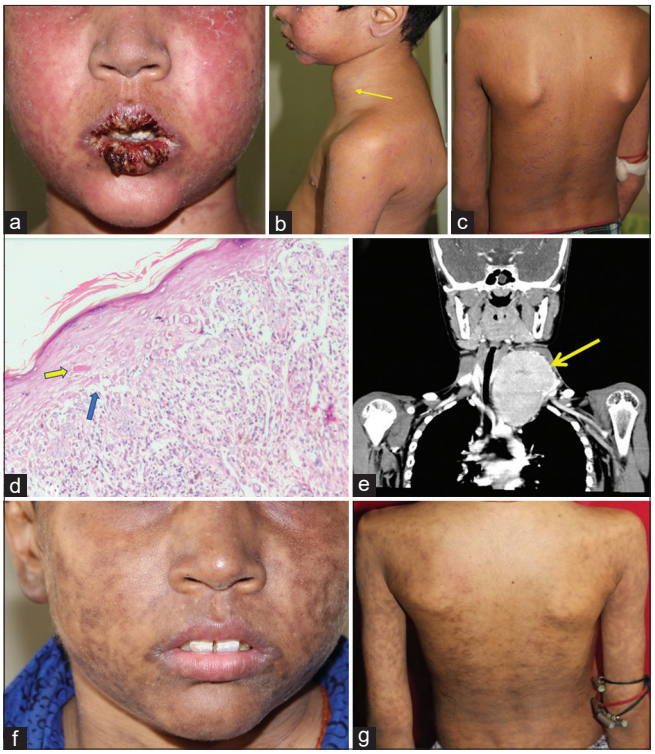

Figure 1: Case-2 (a) with haemorrhagic crusted erosions involving the lips, erythematous to violaceous rash involving the cheeks, (b and c) trunk, limbs and neck swelling (yellow arrow), (d) histopathology showing interface change (blue arrow), mid-spinous apoptotic keratinocytes (yellow arrow) hematoxylin – eosin, 100 × magnification, (e) CT neck showing 5.5 × 4.7 × 7.9 cm intensely enhancing mass in the left cervical region extending into the superior mediastinum, (f and g) follow-up 6 months after surgery - complete healing of lip erosions and post-inflammatory hyperpigmentation

Table 1: Czernik *et al*. criteria for diagnosis of PAMS applied to our patients

Criteria	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Major criteria								
Polymorphous mucocutaneous eruption	+	+	+	+	+	+	+	+
Painful and persistent stomatitis	+	+	+	+	+	+	+	+
Respiratory involvement	-	-	-	+	-	-	-	-
Concurrent internal neoplasia	+	+	+	+	+	+	+	+
Antiplakin antibodies by immunoprecipitation or immunoblotting: 190 kDa (periplakin) and 210 kDa doublet (envoplakin and desmoplakin)	ND*	ND*	ND*	ND*	ND*	ND*	ND*	ND*
Minor criteria								
Acantholysis	+	+	ND*	-	ND*	+	-	-
Subepidermal split	+	+	ND*	+	ND*	-	+	+
DIF showing both intercellular and basement membrane staining patterns	BM†	BM†	BM†	Negative	IC‡	IC‡	IC‡ and BM†	BM†
IIF staining of rodent bladder epithelium	+	ND*	ND*	ND*	ND*	+	ND*	+
Lack of correlation of mucocutaneous disease with anti desmoglein 1 or 3 antibodies	+	+	+	+	+	+	+	+

*ND - Not Done, †BM - basement membrane staining pattern, ‡IC - intercellular staining pattern

Table 2: Clinical and histological features of the patients with PAMS

Age/ Sex	Mucosa/skin involvement	Mucosa O G E	Histopathology	DIF	IIF	Associated neoplasm and tumour status	Treatment	Follow-up and outcome
8/F	PV/LP	+ + +	Intraepidermal acantholysis, Interface dermatitis with thickened basement membrane, SEC	IgG, IgA, IgM, C3 BM, granular	IC	CD (retroperitoneal); complete resection	Prednisolone 1 mg/kg for 5 months followed by 0.5 mg/ kg for 7 months and then slowly tapered and stopped Received methotrexate 10 mg/week for 57 months (from 10th month post-surgery)	112.5 months Remission off therapy
8/M	PV/LP and generalised papular rash	+ - +	Intraepidermal acantholysis, Interface dermatitis, AK, SEC	IgG, IgM, C3 BM, linear	ND	CD (cervical); complete resection	2 mg/kg of prednisolone for a month. Following excision was restarted on 1 mg/kg of prednisolone, tapered and stopped over 10 months	22.5 months Remission off-therapy
28/F	LP/LP	+ - -	ND	IgG, C3 BM, linear	ND	CD (anterior mediastinum), advised excision, lost to follow up	Initiated on 1 mg/kg of prednisolone	2.5 months Partial remission
39/M	LP/-	+ + -	Interface dermatitis, AK, SEC	Negative	ND	NHL; chemotherapy	R-CHOP chemotherapy	3.5 months Expired 20 months after diagnosis
41/F	PV/PV	+ - -	ND	IgG, C3 IC	ND	Thymoma; complete resection + post-operative radiotherapy	Prednisolone 1.2 mg/kg was started after the excision of mass	4 months Partial remission
46/F	PV/LP	+ - +	Intraepidermal acantholysis, Interface dermatitis, AK	IgG, C3 IC	IC	CD (retroperitoneal); complete resection	1 mg/kg of prednisolone for a month before surgery. Following excision was restarted on 1 mg/kg of prednisolone, tapered and stopped over 12 months	5 months Complete remission off-therapy
36/M	LP/-	+ + -	Interface dermatitis, AK, SEC	IgG, C3 IC; IgG, IgM, C3 BM linear	ND	Thymoma; complete resection, post-operative radiotherapy	1 mg/kg of prednisolone, slowly tapered and stopped in a year	38 months Complete remission off-therapy
40/M	PV/LP	+ + -	Interface dermatitis, AK, SEC	IgG, IgM BM linear	IC	CD with FDCS; complete resection	Prednisolone 1 mg/kg was started and advised slow tapering	1 month Partial remission

AK- apoptotic keratinocytes, BM- basement membrane; C3- complement3; CD- Castleman's disease; DIF- direct immunofluorescence; E- eye; F- female; FDCS- follicular dendritic cell sarcoma; G- genital; IC- intercellular pattern; IgA- immunoglobulin A; IgG - immunoglobulin G; IgM- immunoglobulin M; IIF- indirect immunofluorescence; LP- lichen planus; M- male; ND- not done; NHL- non-Hodgkin lymphoma; O- oral; PV- pemphigus vulgaris; SEC-subepidermal clefting

dermatitis (100%) [Figure 1d], (b) mid-spinous apoptotic keratinocytes-5 (83.3%), (c) suprabasal acantholysis-3 (50%), and (d) subepidermal clefting-5 (83.3%). More than one feature was seen in each biopsy [Table 2].

DIF was positive in 7/8 patients and 3 staining patterns were seen [Table 2]: (a) intercellular "fish-net" pattern deposition of IgG or complement (C3) in the epidermis (2/8) (b) granular/linear deposition of IgG or C3 along along the basement membrane zone (4/8), (c) combination of both patterns (1/8). Case-1 with CD who had deposition of IgM, IgG, IGA, C3 with thickened basement membrane on HPE, had positive ANA, anti-dsDNA, and anti-SSA antibodies suggesting overlap with systemic lupus erythematosus (SLE).

IIF on rat bladder was done in 3 patients which showed intercellular "fish-net" fluorescence [Table 2]. Immunoblotting was unavailable in our center and desmoglein levels were not elevated in any of our patients. Three patients with CD and one with thymoma had positive ANA, of whom one was classified as SLE (Case-1), 2 patients (CD-1, thymoma-1) had high anti-dsDNA antibodies and Case-1 had positive anti-tissue transglutaminase antibodies.

Relevant imaging revealed mediastinal mass (3/8), cervical mass extending into superior mediastinum (1/8) [Figure 1e] and retroperitoneal mass (3/8), and the patient with NHL had a conglomerate nodal mass in the peripancreatic, paraaortic and paraceliac region.

Treatment and prognosis

All patients received high dose of systemic steroids ranging from 1 mg to 2 mg/kg for disease control. Case-1 with CD and SLE overlap received methotrexate as a steroid sparing agent. The neoplastic mass was surgically resected in 6/8 patients (CD-4, thymoma-2) and the patient with NHL received R-CHOP (rituximab, cyclophosphamide, vincristine, adriamycin, and prednisolone) chemotherapy. Among the 6 patients who had excision, 2 were operated elsewhere: CD-1, thymoma-1. One patient with CD declined surgical resection and was lost to follow-up. The follow-up period ranged from 1 to 112.5 months (mean, 23.6 months) with a mortality rate of 12.5%. There was a significant clinical improvement [Figure 1f and g] following the removal of the mass, and systemic steroid was tapered and stopped post-operatively over 10-12 months. The combination of medical management with complete surgical resection led to a better prognosis. Case-4 with NHL and bronchiolitis obliterans was planned for autologous stem cell transplant; but he died 20 months after diagnosis [Table 2].

Discussion

In this study, we described the clinical profile of patients with PAMS presenting to a tertiary care center in India and compared it with literature in Table 3.[9-13]

Given the rarity of the condition, most published studies are retrospective.[9-13] Despite PAMS being uncommon in children,[14] we had two children with CD associated PAMS. The most common malignancy associated with PAMS is NHL (38.6%) followed by chronic lymphocytic leukemia (18.4%), CD (18.4%), and thymoma (5.5%).[5] However, CD was the most common neoplasm in our study similar to studies from Taiwan[9] and Korea.[12]

The mucocutaneous manifestations were polymorphic, commonest mucosal, and cutaneous presentation were pemphigus-like and LP-like, respectively. Pemphigus-like presentation was common in other studies.[9-11] LP-like lesions are common in PAMS associated with CD,[2,15] similar to our study. The patients with thymoma had pemphigus-like mucocutaneous presentation and LP-like mucosal presentation each, which are both reported in PAMS associated with thymoma.[9,12] PAMS in children often precedes, and is the presenting sign of occult CD, with a lichenoid pattern akin to our cases.[2,15]

Despite the varied HPE findings, interface dermatitis was consistently seen in all biopsies, as reported by Choi *et al*.[12] The 3 distinct DIF patterns described by Czernik *et al*. include: (i) intercellular, "fish-net" or PV-like (ii) linear or pemphigoid-like basement membrane staining, and (iii) homogenous staining of the entire cell.[5] All patients except for Case-4 with NHL, who was on chemotherapy at presentation, had positive DIF and had the first 2 patterns or a combination of both.

Tumour cells cause cytokine dysregulation leading to autoantibody production and induction of cytotoxic autoimmunity.[5] Several studies have proven that autoantibodies against plakins are mainly implicated in the pathogenesis of PAMS. The epitope mapping of Dsg3 and IgG isotype profile of PAMS is distinct from pemphigus vulgaris[16] and association between antibodies to Dsg1 or Dsg3 and clinical phenotype is not established,[10] as in our study.

Castleman's disease is a rare lymphoproliferative disorder, commonly located in the mediastinum or retroperitoneum. CD could be single site or multicentric; hyaline vascular, plasma cell, or mixed based on histology.[2] All our patients with CD had hyaline vascular variant and one developed additional sarcomatous changes. Cells of CD express high levels of IL-6, which is associated with multiple autoimmune

Table 3: Comparison of present study with published literature on PAMS

Characteristic	Present study	Cho *et al*. 2014[9]	Ohyama *et al*. 2001[10]	Leger *et al*. 2012[11]	Choi *et al*. 2012[12]	Fournet *et al*. 2018[13]
Country of study	India	Taiwan	United States and Japan	France	Korea	France
Number of patients	8	11	21	53	12	7
Mean age (in years)	31	62	50	59 (median)	45	64 (median)
Number of children	2	0	0	0	0	0
First two commonly associated neoplasms	CD Thymoma	CD Thymoma	Malignant lymphoma CLL	CLL NHL	CD FDCS	Carcinomas
Mucosal involvement						
Oral	100	100	100	89	92	86
Genital	50	45	57	51	58	57
Ocular	38	36	81	53	58	29
Most common skin lesion	LP-like	Pemphigus-like	Pemphigus-like	Pemphigus-like	EM-like	Pemphigus-like
Mortality rate	12.5%	64%	NA	68%	50%	14.3%

CD - Castleman's disease; CLL - chronic lymphocytic leukemia; EM - erythema multiforme; FDCS - follicular dendritic cell sarcoma; NA - not available; NHL - non-Hodgkin lymphoma

phenomena like SLE, Sjögren syndrome, cytopenia, peripheral neuropathy and PAMS,[2] which was evident among our patients.

Overall, the prognosis of PAMS is poor with a 90% mortality rate. They can develop bronchiolitis obliterans, with a constrictive and obstructive pattern of respiratory failure, which is the commonest cause of mortality.[5] Most patients die due to respiratory failure, sepsis, underlying neoplasm, or treatment complication.[5] Mortality is significantly reduced if the neoplastic mass is circumscribed and resected timely.[17] Timely detection and resection of the neoplasm, and early initiation of treatment improved the outcome in our patients as shown by Zhang *et al*.[17] Mortality rate as high as 70% has been reported in children with PAMS due to CD, of whom 90.5% has respiratory involvement and 81% died of respiratory failure.[15] However, our children with CD had good prognosis. Our mortality rate was 12.5% (1/8) secondary to respiratory involvement in a patient with nonresectable malignancy (NHL).

Limitations

Retrospective nature from a single center and lacunae in information collection in few patients were the limitations. Investigations were not uniformly done for all patients and the facility for immunoblotting was unavailable.

Conclusion

Our study describes the clinical profile of PAMS from India. The most common associated neoplasm was CD followed by thymoma. Polymorphic mucocutaneous manifestations with predominant pemphigus-like or LP-like features, intractable stomatitis with vermilion border involvement, histology showing a combination of acantholysis, keratinocyte necrosis, and interface dermatitis should raise a suspicion of PAMS, warranting detailed paraneoplastic evaluation. Early diagnosis is crucial as timely resection of neoplasm and initiation of systemic treatment improves the overall outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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