Biomedical & Pharmacology Journal, June 2025. Vol. **18**(2), p. 1750-1758

The Five-Year Abdominal Pain Conundrum - A Bizarre Case of Secondary Amyloidosis

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https://dx.doi.org/10.13005/bpj/3211

(Received: 14 September 2024; accepted: 10 March 2025)

Amyloidosis is a vast group of diseases associated with a number of inherited and inflammatory disorders which is marked by extracellular fibrillar proteins leading to tissue damage. There are various biochemical types of amyloid proteins which along with the clinical signs are used in classifying this condition into- AL Amyloidosis, A Beta Amyloidosis, AA Amyloidosis, AE amyloidosis so on and so forth. Amyloidosis is usually diagnosed by demonstrating amyloid deposits in the tissues by various diagnostic modalities like pathological and immunohistochemical studies. The management of amyloidosis involves symptomatic treatment and targeting the underlying cause. Ideally, prompt diagnosis and treatment of the underlying cause can prevent the development of secondary amyloidosis. Timely intervention and management of amyloidosis will improve the quality of the patient's life. Informed consent obtained from patient guardians. A 31yr old male from Tamil Nadu had experienced several episodes of fever and abdominal pain on and off for almost five and a half years. He underwent various investigations throughout those years starting with baseline investigations such as CBC, ESR, CRP, etc. to high end investigations like bone marrow biopsy and renal needle biopsy. He underwent several other procedures like diagnostic laparoscopy of abdomen and right hemicolectomy. He was then suspected to have secondary amyloidosis with familial mediterranean fever as the probable underlying cause. After all those years of symptomatic management, he was started on colchicine along with steroid and was advised gene study by the end of the year 2008. Years of delay in arriving to a final diagnosis led to his premature demise. We report a case of secondary amyloidosis in which familial Mediterranean fever is most likely the underlying aetiology. When treating recurrent episodes of abdominal pain with fever, it is crucial to understand the significance of FMF as a differential diagnosis, despite its rarity.

Keywords: Amyloidosis; Colchicine; Chronic Abdominal pain; Familial Mediterranean Fever; Non-Ulcer Dyspepsia.

Secondary amyloidosis, also known as reactive amyloidosis, is a systemic condition characterized by the extracellular deposition of amyloid fibrils derived from serum amyloid A (SAA) protein. This disorder typically occurs as a complication of chronic inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, or chronic infections like tuberculosis.[1-3] The accumulation of amyloid fibrils in various organs, including the kidneys, liver, spleen,

and heart, can lead to significant morbidity and mortality.[4,5]

The underlying pathophysiology involves a prolonged inflammatory state that stimulates hepatocytes to produce excessive SAA protein. In genetically predisposed individuals, this SAA undergoes proteolytic cleavage and misfolding, forming insoluble amyloid deposits.[6] The clinical presentation of secondary amyloidosis is highly variable, often reflecting the affected organ systems. Renal involvement is particularly common and manifests as proteinuria, which may progress to nephrotic syndrome or end-stage renal disease.[7,8] Early diagnosis and effective management of the underlying inflammatory condition are critical to preventing further amyloid deposition and organ damage.[9]

Recent advances in imaging techniques, such as SAP scintigraphy, and biomarkers, including SAA levels, have improved diagnostic accuracy.[10] Additionally, therapeutic strategies targeting the reduction of SAA levels and the inhibition of amyloid fibril formation, such as biologics and small-molecule inhibitors, are promising avenues of research.[4,11] Despite these advances, the prognosis remains poor in patients with advanced organ involvement, emphasizing the importance of timely intervention.

This case study highlights a clinical scenario of secondary amyloidosis in a patient with chronic inflammatory disease, emphasizing the challenges in diagnosis and management. Through a detailed exploration of clinical findings, diagnostic evaluations, and treatment approaches, we aim to provide insights into improving patient outcomes and raising awareness about this rare but serious complication.

Objective

Our objective is to emphasize the need for early and accurate diagnosis of underlying cause of Secondary Amyloidosis.

MATERIALS AND METHODS

Case Presentation

In October of 2003, a 26-year-old male presented to his physician with complains of fever and abdominal pain on and off for a week. Relevant laboratory investigations were performed and his results were as follows Hb- 12.5 gm%, Stools- no occult blood. He was also tested for Typhoid and Malaria which revealed a negative result.

Oesophagogastroduodenoscopy revealed prepyloric gastric ulcer. Patient was treated with T. Rabeprazole for 2 months. A repeat oesophagoduodenoscopy and an abdominal ultrasound was performed in July 2004 as his symptoms recurred. Ultrasound showed no significant abnormalities while the Oesophagogastroduodenoscopy showed lax lower oesophageal sphincter, suggestive of Gastro-oesophageal reflux. He was advised to take Tab. Rabeprazole as needed.

In February of 2005, he presented to his gastroenterologist with intermittent periumbilical pain for 10 days with loss of weight inspite of normal appetite. On examination, mild pallor was noted. Laboratory tests revealed low haemoglobin levels and elevated acute phase reactants. Anti-TB IgM was equivocal. He was also tested for Tuberculosis.

Ultrasound was found to be normal. He was diagnosed with Non-Ulcer Dyspepsia with Non erosive reflux disease. As he also complained of lower back ache and right loin pain, he was referred to a Rheumatologist. He was found to have positive family history of Ankylosing Spondylitis in his father. Patient was suggested to take X-rays of Pelvis and LS spine which did not reveal any findings.

Owing to his unremitting symptoms, he was admitted for Chronic abdominal pain for evaluation and planned for Diagnostic Laparoscopy and lymph node biopsy in March of 2005. Laparoscopic findings were indicative of right iliac fossa mass with omental adhesions, terminal ileal mass with stricture. Ileocaecum and appendix were found to be normal. Biopsy of omentum and peritoneum showed no specific pathology. Biopsy of mesenteric lymph node showed chronic non-specific lymphadenitis, suggesting the possibility of tuberculous lymph node. However, there was no frank evidence of tubercle in all the three specimens studied. Patient was put on a 4 drug ATT regimen along with 2 months of steroid.

Despite treatment, the patient's symptoms persisted. In June of 2005, Diagnostic laparoscopy was planned due to his unwaning symptoms. However, patient was taken for emergency right hemicolectomy. The following specimens were

sent for biopsy: Terminal portion of ileum- 22cm, Caecum with ascending colon with appendix, along with flat piece of fibrofatty tissue, and 9 pericolic lymph nodes. Macroscopically, Ileal mucosa showed focal ulcerations. Caecum showed a nodular area in mucosal aspect measuring 2 x 1.5 x 1.5 cm. Adjacent to the nodular area, an ulcer measuring 1.5 x 1.5 cm involving the ileocaecal junction with brown material in the floor. Lymph nodes appear greyish brown on dissection. Microscopically, small intestine wall showed foci of ulceration with marked increase in laminar propria cellularity by lymphocytes, some plasma cells, neutrophils, and in between these nodules, foci of extensive mucosal ulcerations with underlying muscularis showing discontinuity. There is marked fibrosis of the wall. Similar microscopic findings were noted in the nodularity of the caecum. The ileocaecal junction wall showed extensive mucosal ulceration with acute inflammatory exudate overlying inflammatory granulation tissue composed of proliferative red vessels with similar infiltrates. The muscle coat is discontinuous. The appendix showed submucosal enlarged lymphoid follicles with prominent reactive germinal centre. Similar enlarged follicles with prominent reactive germinal centre were seen in the lymph nodes. The fibroadipose tissue showed some fibrosis with focal inflammatory granulation tissue with proliferated blood vessels and cellular infiltrates. The proximal and distal resection margin showed no lesions. These findings were suggestive of nonspecific subacute inflammatory ulcers with eosinophilia and marked fibrosis in the ileocaecal region; nonspecific reactive lymphoid hyperplasia. These specimens were sent to a different histopathology laboratory for a second opinion. They noted ileum showing segments of firm strictured areas with narrow lumen and thickened wall showing haemorrhagic foci within it. The mucosa of the intestine was found to be oedematous with hypoxic changes microscopically. The lamina propria showed dense acute on chronic inflammatory reaction. Submucosa and muscle were destroyed by the presence of abscess showing dense acute on chronic inflammatory reaction with granulation tissue formation. Extensive serositis with peritonitis and adhesions present. No granulomas were noted. These findings suggested severe acute inflammation abscess formation of the small intestine with severe peritonitis and serositis with adhesions. No evidence of TB, amoebiasis, Crohn's disease, or malignancy were noted. He was tested for Brucella which showed negative result.

In September of 2007, patient presented to a different gastroenterologist with increased frequency of stools, pain localised to epigastric region, nausea, belching, regurgitation, bloating on and off for two years. On per rectal examination, bleeding was noted. On examination mild pallor was observed. Patient also presented with multiple aphthous ulcers, and glossitis. He was advised to undergo a colonoscopy, upper GI endoscopy, enteroscopy, and rectal mucosa biopsy.

On biopsy, oedema and congestion of colonic and gastric mucosa was observed. Tiny pale white 2mm nodules embedded in toto were seen in the rectal mucosa, microscopically extensive autolytic changes noted in colonic mucosa and rectal mucosa. Patient was advised to take tests for pANCA and ASCA to rule out Ulcerative Colitis which revealed negative result.

These findings were suggestive of the underlying aetiology probably being Ulcerative Colitis as Crohn's disease was ruled out earlier in the biopsy. The patient had Grade A reflux esophagitis with erosive antral gastritis and non-specific colitis. He was initiated on a trial of tablet Mesalazine, Prednisolone, tablets Folic Acid and other vitamin supplements, Calcium, Rabeprazole and Domperidone.

Symptomatically, patient's condition deteriorated. In May of 2008, a series of tests were performed which revealed his total protein levels and haemoglobin had dropped. Tests revealed proteinuria and elevated acute phase reactant proteins. Leptospira was found to be negative. He was suspected to have a mild exacerbation of Ulcerative Colitis. ANA was negative. PT- 11.6 s, APTT- 34 s, INR <1.

Serum complement levels were: C3- 1.12 g/dL, C4- 0.45 g/dL. Patient was admitted for proteinuria under evaluation. A USG guided renal needle biopsy showed deposits of a smooth eosinophilic weakly PAS positive homogenous material in the mesangium and around the vascular pole of glomerulus. Focal minimal tubular atrophy along with some interstitial round cell infiltrated were noted. Congo red stain showed

greenish bifringence under polarised light. Immunofluorescence showed granular minimal deposits of IgM and C3c. These findings suggested Renal Amyloidosis- AA type. Radiographic tests were performed. CT Chest showed signs of moderate pleural effusion with left lingular segment patchy fibrosis.

July of 2008, he developed bloody diarrhoea. Haemoglobin levels were 8.6 g/dL. Small bowel enema showed mucosal thickening of jejunal loops. Bone density scans were suggestive of osteoporosis. Serum Ferritin- 17.29 ng/mL. CA 19.9- 22.29 U/L. Fibrinogen and Clotting activity- 576 mg/dL, which was highly elevated. Platelet count was- 670,000 /mm^3. CMV IgG antibody- 6.03 U/mL. Stool culture was insignificant. Oesophago gastroduodenoscopy and jejunoscopy was done and biopsies from stomach, jejunum, ileum, colon, and rectum showed features suggestive of Amyloidosis- Non-AA. These specimens were reviewed in a different histopathology laboratory and these were the following findings. Gastric biopsy showed pepsin secreting cell hyperplasia secondary to proton pump inhibitor therapy. Duodenum /Jejunum biopsy showed extensive partial to total mucosal atrophy with eosinophilia which indicates malabsorption syndrome. Colitis with ulceration and vascular changes secondary to amyloidosis was revealed in colon biopsy. Kidney biopsy and colon biopsy showed features compatible with amyloidosis. Urine for Bence jones protein was negative. Renal needle biopsy and endoscopic biopsy of ileum showed characteristics of secondary amyloidosis. Bone marrow aspiration revealed cellular marrow showing decreased iron and non-specific reactive changes [mild myeloid hyperplasia with toxic change and mild plasmacytosis]. Inference being mildly hypercellular marrow with mild myeloid hyperplasia. Immunofixation test showed normal IFE levels. Anti-tissue transglutaminase antibody was negative.

Platelet was 6,44,000/mm^3 and PT INR were 16.8 sec and 1.40 sec respectively. Test for immunoglobulins – Ig G, Ig A and Ig M were done and was found to be 242 mg%, 71 mg% and 74 mg% respectively. Further testing showed low TIBC, Iron, Ferritin, Vit B12 levels and normal folate levels. Blood picture was positive for anisocytes, microcytes, acanthocytes and toxic changes. He was referred to a haematologist and was diagnosed to have secondary amyloidosis with anasarca, with the underlying aetiology to have likely been Familial Mediterranean Fever. His grandfather had previously passed away due to abdominal pain and fever of unknown origin. He was advised to do amyloid scinti scan, biochemical analysis for amyloid, gene study for FMF and trial for colchicine- 0.5 mg. The patient was started on colchicine twice daily along with various supplements like folic acid, cobalamin, and regular iron sucrose infusions. He was also advised PRBC transfusion for two days. MRI LS spine revealed minimal oedema of posterior paraspinal muscle,

Table 1. Widal slide agglutination test

Widal slide agglutination	Value
S. Typhi O	Negative 1:20 dilution
S. Typhi H	Negative 1:20 dilution
S. Paratyphi AH	Negative 1:20 dilution
S. Paratyphi VH	Negative 1:20 dilution

Table 2. Malarial parasite test by QBC, smear

Tests for Malarial Parasite	Value
QBC – MP, MF	Not seen
Smear- MP, MF	Not seen

Table 3. Test for tuberculosis

Tests for Tuberculosis	Value
Anti- TB IgM (Ref value: <1 Units)	1 (equivocal)
PCR for MTB -Blood	Negative

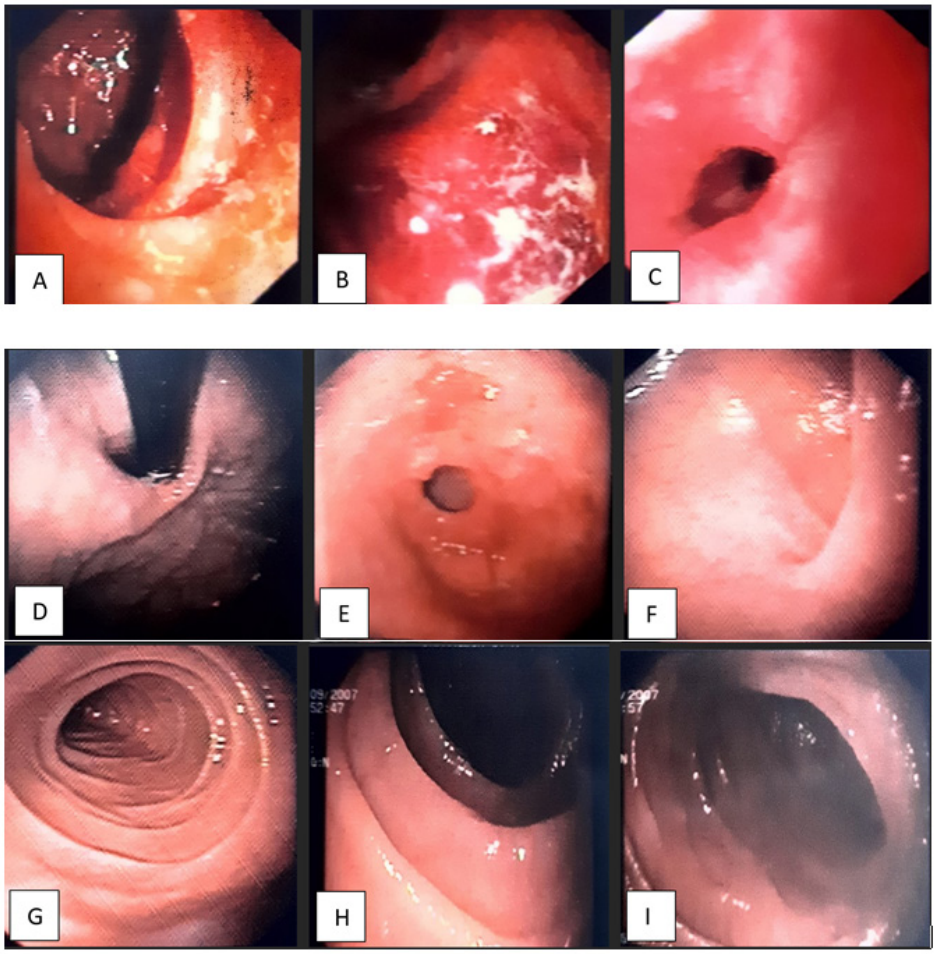
Table 4. Test for Brucella antibodies.

Brucella antibodies (Tube method)	Value
Antibodies to Brucella abortus	1:40
(Significant titres- 1:80)	(Not significant)
Antibodies to Brucella melitensis	1:40
	(Not significant)

gluteal muscle and muscles of flexor compartment of bilateral thigh – probably myositis. Diffuse oedema of subcutaneous fat, minimal ascites and minimal bilateral pleural fluid. Repeated RFT, LFT and CBC were performed on daily basis which showed progressive decline of renal and hepatic functions. While on colchicine therapy, gene test for MEFV mutation was sent to prove the underlying aetiology of secondary amyloidosis to be Familial Mediterranean Fever. However, due to his deteriorating physical condition the patient passed away prior to confirmation.

RESULTS AND DISCUSSION

Secondary amyloidosis (AA amyloidosis) is a severe systemic condition arising as a complication of chronic inflammatory or infectious diseases. It is characterized by the deposition of fibrils composed of serum amyloid A (SAA) protein in various organs, leading to progressive dysfunction.[12] In this case, delayed diagnosis resulted in the patient's demise before treatment could be initiated, highlighting significant diagnostic and therapeutic challenges in AA amyloidosis.



A&B: Whole colon upto proximal part of the ascending **colon** mucosa showed severe erythema with small ulcers which bleed on touch but haustrations were maintained. C: Hyperemic lower third of **esophagus** with lax LES. D: **Fundus-** normal. E: **Antrum-** congested with multiple small erosions. F: **First part of Duodenum-** normal. G: **Second part of Duodenum-** normal. H&I: **Jejunum-** Mucosa healthy. No polyp. No ulcers. No growths.

Fig. 1. Colonoscopy, Upper GI Endoscopy, Enteroscopy, and rectal mucosa biopsy reports

The clinical presentation of secondary amyloidosis varies widely, depending on the organs involved. Renal involvement, marked by proteinuria, nephrotic syndrome, and eventual kidney failure, is the most common manifestation.[13-15] Other organs, including the gastrointestinal tract, liver, spleen, and heart, may also be affected, contributing to a range of nonspecific symptoms such as weight loss, fatigue, and abdominal discomfort.[16,17] This variability often complicates early diagnosis. In our patient, a prolonged history of inflammatory disease with systemic symptoms was present, but the lack of timely investigative focus delayed the recognition of amyloidosis.

Timely diagnosis of AA amyloidosis depends on maintaining a high index of suspicion, particularly in patients with chronic inflammatory conditions.[18] Tools such as tissue biopsy with Congo red staining, serum amyloid P component scintigraphy, and measurement of circulating SAA levels are crucial for confirming the diagnosis.[19-21] However, accessibility to specialized diagnostic tests and the need for clinical expertise often result in diagnostic delays, as seen in this case.

The management of AA amyloidosis hinges on controlling the underlying inflammatory disease to reduce SAA production and halt amyloid deposition.[22] Anti-inflammatory therapies, such as biologics targeting cytokines like tumor necrosis factor-alpha (TNF-á) or interleukin-6, have shown efficacy in mitigating disease progression.[23,24] However, once significant organ damage has occurred, prognosis worsens dramatically, underscoring the importance of early intervention. Our case illustrates how the lack of early diagnostic and therapeutic strategies can lead to fatal outcomes.

Table 5. Blood immunology test report

Blood Immunology	Value
pANCA (IFA method)	Negative
ASCA IgARef. Value: >25 U/mL	29.6
ASCA IgGRef. Value: >25 U	30.4

Table 6. Protein electrophoresis test

Protein Electrophoresis	Observed values
Total protein(Ref Value- 6.6-8.8 g/dL)	4.4
Albumin(Ref Value- 52-65%)	32.6
α_1 Globulin(Ref Value- 2.5-5.0%)	3.2
α_2 Globulin(Ref Value- 7-13%)	37.9
β Globulin(Ref Value- 8-14%)	18.8
γ Globulin(Ref Value- 12-22%)	7.5
A:G	0.48

Table 7. CBC test values

Investigations	Observed Values												
	Oct 2003	Feb 2005	March 2005	June 2005	Sept 2005	Aug 2007	Sept 2007	5.05. 2008	20.05. 2008	14.07. 2008	2008 06.09. 2008	08.09. 2008	17.11. 2008
Haemoglobin (N- 13.5-17 g/dL)	12.5	11.4	13	11		11.1	10	9.8	9.6	8.6	8.7	7.2	9.1
PCV(N- 35-42%)	36.6		41	35					32.8	30			27.3
ESR(N- 15mm at the end of 1hr)	100	78			68	72	112	129	122				100

Table 8. Immunofixation test

Serum free Kappa chains and Lambda chains	Observed values
Kappa (Ref. Value- 3.3-19.4 mg/L)	20.2
Lambda (Ref. Value- 5.7-26.3 mg/L)	15.9
Kappa: Lambda (Ref. Value- 0.26-1.165)	1.2

Emerging therapies targeting the amyloidogenic process itself, such as fibril inhibitors and agents promoting fibril resorption, offer hope for future management.[25] Additionally, improved diagnostic protocols incorporating imaging modalities like positron emission tomography (PET) and biomarkers such as urinary proteomics may aid in earlier detection.[26] Enhanced awareness among healthcare providers

Table 9. Serum protein, albumin, globulin, urine albumin. The serum protein and albumin was found to be decreasing from 2003 to 2008

Investigations	Observed Values									
	Oct 2003	Feb 2005	March 2005	May 2005	Sept 2007	May 2008		June 2008	Sept 2008	Nov 2008
						5/05	20/05			
Serum Protein (N- 6-7.8 g/dL)		7.1		7	7.4	5.8	5.1	4.3	3.3	2.6
Serum Albumin (N-3.8-5.0 g/dL)		3.7		3.6	3.1	2.1	2.3	2	1.3	0.9
Serum Globulin (N- 2.3- 3.5 g/dL)		3.4		3.4	4.3	3.7	2.8	2.3	2.0	1.7
Urine Albumin (N- negative)	Negative		Negative	Negative	++++	+++				+++
24 hr Urine Protein						1.8 g/day			11.3 g/day	

about the risk factors and clinical presentations of AA amyloidosis is essential to address diagnostic delays.

This case underscores the critical need for vigilance in patients with chronic inflammatory diseases. Despite advances in understanding amyloidosis, gaps in awareness and diagnostic approaches persist. Addressing these gaps requires education, improved access to diagnostic tools, and the development of standardized screening protocols for at-risk populations. Ultimately, a multidisciplinary approach involving primary care, rheumatology, nephrology, and pathology is key to improving outcomes in AA amyloidosis.

CONCLUSION

Secondary amyloidosis is a serious and often fatal condition resulting from chronic inflammatory diseases, frequently complicated by delayed diagnosis and multisystem involvement. In this patient, the advanced stage of organ dysfunction underscored the critical need for timely recognition and intervention. Emerging research highlights the potential role of the anti-aging gene, Sirtuin 1 (SIRT1), in modulating inflammatory responses, preventing organ damage, and promoting cellular survival. SIRT1 has shown promise in attenuating oxidative stress, reducing inflammatory cytokine activity, and mitigating programmed cell death, all of which are implicated in the progression of secondary amyloidosis.[27,28,29] Future therapies targeting SIRT1 activation may offer a novel strategy to reverse multi-organ dysfunction and improve outcomes in patients with systemic amyloidosis.

ACKNOWLEDGEMENT

Authors acknowledge the Department of Biochemistry, Departments of General Medicine, Sree Balaji Medical College, and Hospital for the support in successfully presenting this case study.

Funding sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest

The author(s) do not have any conflict of interest.

Data availability statement

This statement does not apply to this article.

Ethics statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Infromed consent statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical trial registration

This research does not involve any clinical trials

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Not Applicable.

Authors contribution

Dr. K. Sumathi wrote this case study; Dr. Samyuktha Thadderina A, Dr. Saranmani Jyotsna Kumaran, Dr. Mary Chandrika Anton, Dr. B. Shanthi helped with the discussion

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