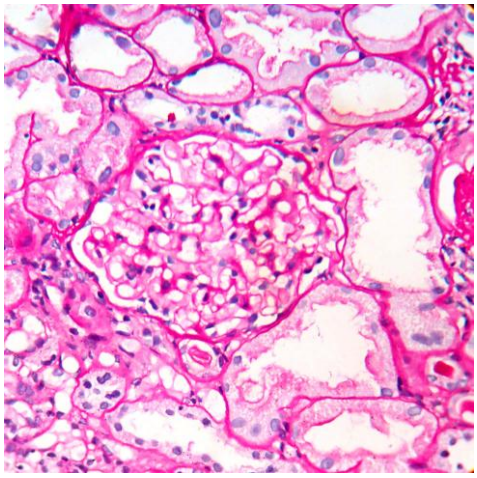
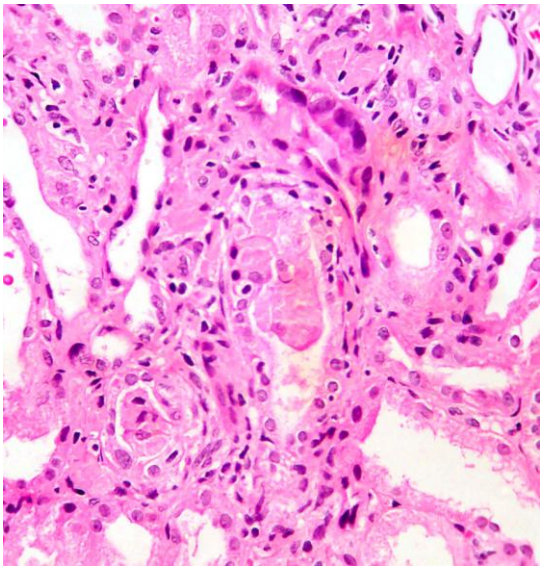
www.nephro-pathology.com

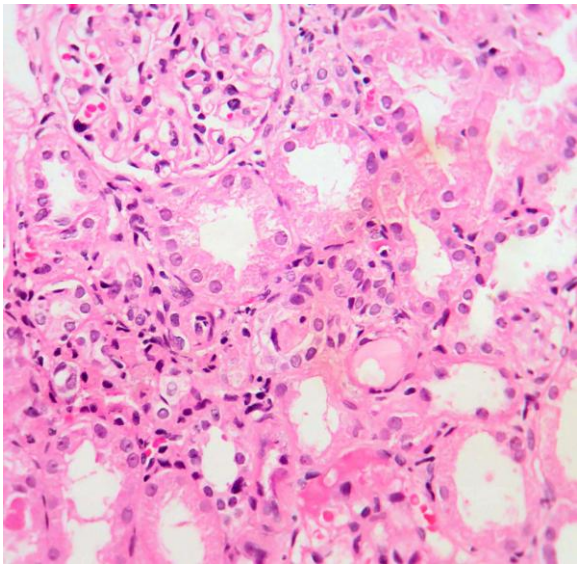
Case of the Month 13

56 year old female with renal dysfunction, subnephrotic proteinuria glucosuria and distal renal tubular acidosis. Renal biopsy was performed.

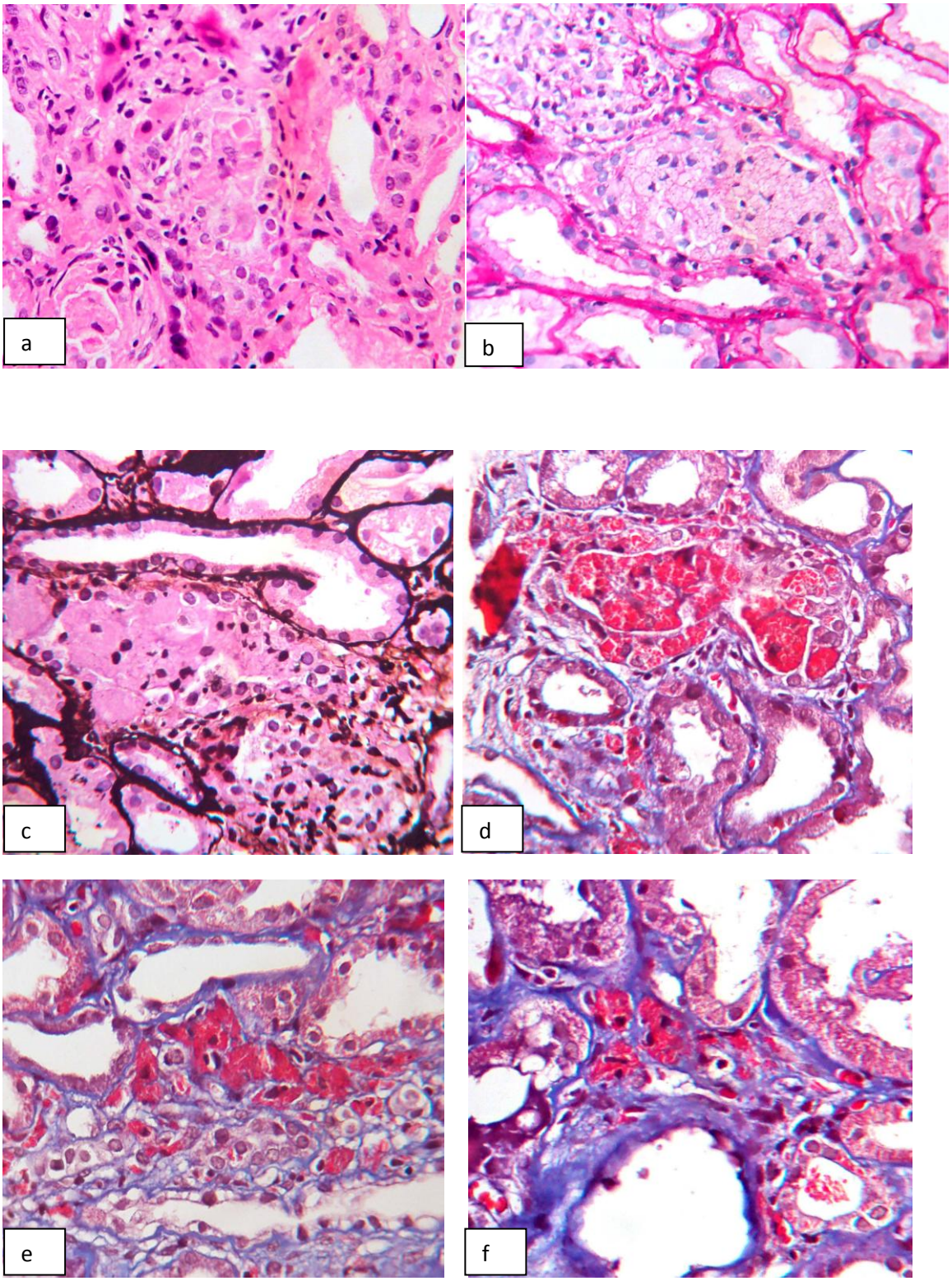


Unremarkable appearing glomerulus.





Granular casts in tubular lumina and interstitial histiocytic aggregates containing crystalline material



Tubular cytoplasmic crystalline inclusions (rhomboid shaped crystal in first left panel photomicrograph) and histiocytic aggregates with cytoplasmic material what is PAS negative (b), silver negative (c) and intensely fuchsinophilic with Masson's Trichrome stain (d-f).

No tissue could be sampled for DIF and EM examination. On basis of morphological findings, evaluation for plasma cell dyscrasia/ hematologic monoclonal proliferations was advised which revealed and IgG lambda type monoclonal paraprotein in serum & urine immunoelectrophoresis, raised concentration of serum lambda light chains and bone marrow plasmacytosis of 35%.

FINAL DIAGNOSIS: Renal Crystal storing histiocytosis associated with a systemic (multiple) myeloma (IgG lambda)

DISCUSSION:

Crystal-storing histiocytosis (CSH), a rare condition in which crystalline material accumulates in the cytoplasm of histiocytes, is typically associated with disorders that express monoclonal immunoglobulins, such as multiple myeloma (MM), lymphoplasmacytic lymphoma (LPL), and monoclonal gammopathy of undetermined significance (MGUS).

In a review by Dogan et. al about 80 cases of CSH occurring in various organs were reviewed from the available literature, among these only five were reported primarily in the kidney.

The exact mechanism for crystal formation in CSH is not well understood and may involve multiple factors, including overproduction to abnormal secretions to impaired excretion of immunoglobulins. Crystallogenesis is more related to the type of light chain rather than to a specific heavy chain . CSH occurring in some patients with proximal renal tubular dysfunction (Fanconi syndrome) does add credence to the hypothesis that in some instances CSH may be due to decreased excretion of immunoglobulins . Lebeau et al. examined the molecular configuration of a stored kappa light chain in a 73-year-old man with G-CSH associated with monoclonal gammopathy and observed that the light chain was structurally altered by several amino acid substitutions. They postulated that conformational alteration induced by the abnormal amino acid sequences was a probable crucial factor in the pathogenesis of CSH, promoting crystallization of the protein or adversely affecting its intralysosomal degradation or both. Whether chemotherapy might have a similar structural affect on proteins and elicit the formation of CSH in some patients with a LP-PCD is uncertain.

Pathologists should be aware of several caveats in diagnosis of CSH. Not infrequently the cytoplasm of the histiocytes is so deeply eosinophilic and opaque that it will obscure any inclusions, crystals, or striations on microscopic examination resulting in a missed diagnosis. Likewise, in most cases of CSH, the histiocytic component is dominant and, as such, may mask the neoplastic nature of any background lymphocytes or plasma cells. And lastly, in exceptional cases, there may be discordance between the clonality of the crystals and the serum; for example, the crystals may appear polyclonal on immunostaining while a monoclonal protein is apparent in the serum.

CSH may also occur in setting of benign conditions including cases described with Clofazimine administration (anti tubercular drug), Charcot Leyden crystal accumulation, use of silica as sclerosing agents (as in hernia repair) and in hereditary cystinosis. Dogan et.al have also proposed a classification for various forms of CSH (Table)

Table 1 Proposed classification of CSH

According to etiology and/or associated disease	According to crystal
1. Hematopoietic	1. Immunoglobulin
A. Multiple myeloma	A. Type
B. Extramedullary plasmacytoma	(1) Heavy chain
C. Lymphomas	(2) Light chain
	B. Clonality
2. MGUS-Amyloid	(1) Monoclonal
	(2) Polyclonal
3. Drugs	(3) Indeterminate
A. Clofazimine	
	2. Clofazimine
4. Allergic-autoimmune	
A. Rheumatoid arthritis	3. Charcot-Leyden
B. Eosinophilic colitis	
C. Mastocytosis	4. Other
D. Hypereosinophilic syndrome	A. Cystine
	B. Silica
5. Metabolic	
A. Cystinosis	
6. Inflammatory-reactive	
A. Pulmonary infections	
B. Plasma cell granuloma	
C. Crohn's disease	
D. *Helicobacter pylori*	
7. Other	
A. Silica	

CSH crystal-storing histiocytosis, *MGUS* monoclonal gammopathy of undetermined significance

Selected References:

1. Kapadia SB, Enzinger FM, Heffner DK, Hyams VJ, Frizzera G. Crystal-storing histiocytosis associated with lymphoplasmacytic neoplasms. Report of three cases mimicking adult rhabdomyoma. Am J Surg Pathol. 1993;17:461–7.
2. Lebeau A, Zeindl-Eberhart E, Muller E-C, Muller-Hocker J, Jungblut PR, Emmerich B, Lohrs U. Generalized crystal-storing histiocytosis associated with monoclonal gammopathy: molecular analysis of a disorder with rapid clinical course and review of literature. Blood. 2002;100:1817–27
3. Jones D, Bhatia VK, Krausz T, Pinkus GS. Crystal-storing histiocytosis: a disorder occurring in plasmacytic tumors expressing immunoglobulin kappa light chain. Hum Pathol. 1999;30:1441–8.
4. Gebrail F, Knapp M, Perrotta G, Cualing H. Crystalline histiocytosis in hereditary cystinosis. Arch Pathol Lab Med. 2002; 126(9):1135.

5. Lewis JT, Candelora JN, Hogan RB, Briggs FR, Abraham SC. Crystal-storing histiocytosis due to massive accumulation of Charcot-Leyden crystals: a unique association producing colonic polyposis in a 78-year old woman with eosinophilic colitis. Am J Surg Pathol. 2007;31:481–5.
6. Sukpanichnant S, Hargrove NS, Kachintorn U, Manatsathit S, Chanchairujira T, Siritanaratkul N, Akaravipuyh T, Thakerngpol K. Clofazimine-induced crystal-storing histiocytosis producing chronic abdominal pain in a leprosy patient. Am J Surg Pathol. 2000;24:129–35.
7. Bosman C, Camassei FD, Boldrini R, Piro FR, Saponara M, Romeo R, Corsi A. Solitary crystal-storing histiocytosis of the tongue in a patient with rheumatoid arthritis and polyclonal hypergammaglobulinemia. Arch Pathol Lab Med. 1998;122:920–4.
8. Colby TV, Koss MN, Travis WD. Tumors of the lower respiratory tract. Washington, DC: Armed Forces Institute of Pathology; 1995. Atlas of tumor pathology, 3rd series, fascicle 13.
9. Coupland SE, Foss HD, Hummel M, Stein H. Extranodal marginal zone B-cell lymphoma of the lacrimal gland associated with crystal-storing histiocytosis. Ophthalmology. 2002;109:105–10.
10. De Alba Campomanes AG, Rutar T, Crawford JB, Seiff S, Goodman D, Grenert J. Crystal-storing histiocytosis and crystalline keratopathy caused by monoclonal gammopathy of undetermined significance. Cornea. 2009;28(9):1081–4.
11. De Lastours V, Papo T, Cazals-Hatem D, Eden A, Feydy A, Belmatoug N, Chauveheid MP, Lidove O, Fantin B. Bone involvement in generalized crystal-storing histiocytosis. J Rheumatol. 2006;33(11):2354–8.
12. El Hamel C, Thierry A, Trouillas P, Bridoux F, Carrion C, Quellard N, Goujon JM, Aldigier JC, Gombert JM, Cogne´ M, Touchard G. Crystal-storing histiocytosis with renal Fanconi syndrome: pathological and molecular characteristics compared with classical myeloma-associated Fanconi syndrome. Nephrol Dial Transplant. 2010;25(9):2982–90. Epub 2010 Mar 31.
13. Fairweather PM, Williamson R, Tsikleas G. Pulmonary extranodal marginal zone lymphoma with massive crystal storing histiocytosis. Am J Surg Pathol. 2006;30:262–7.
14. Farooq U, Bayerl MG, Abendroth CS, Verma C, Talamo G. Renal crystal storing histiocytosis in a patient with multiple myeloma. Ann Hematol. 2009;88:807–9.
15. Pitman SD, Wang J, Serros ER, Zuppan C. A 70-year-old woman with acute renal failure. Crystal-storing histiocytosis. Arch Pathol Lab Med. 2006;130:1077–8.
16. Sethi S, Cuiffo BP, Pinkus GS, Rennke HG. Crystal-storing histiocytosis involving the kidney in a low-grade B-cell lymphoproliferative disorder. Am J Kidney Dis. 2002;39:183–8.
17. Stokes MB, Aronoff B, Siegel D, D'Agati VD. Dysproteinemia related nephropathy associated with crystal-storing histiocytosis. Kidney Int. 2006;70:597–602.
18. Tomioka M, Ueki K, Nakahashi H, Isoda A, Kuroiwa T, Kaneko Y, Hiromura K, Nojima Y. Widespread crystalline inclusions affecting podocytes, tubular cells and interstitial histiocytes in the myeloma kidney. Clin Nephrol. 2004;62:229–33.