Glucocorticoid-dependent Tubulointerstitial Nephritis with IgM-positive Plasma Cells Presenting with Intracellular Crystalline Inclusions within the Rough Endoplasmic Reticulum

Masanori Minato¹, Taichi Murakami¹², Naoki Takahashi¹, Hiroyuki Ono¹, Kenji Nishimura¹, Masanori Tamaki¹, Kojiro Nagai¹, Hideharu Abe¹, Masayuki Iwano³, Kensuke Joh² and Toshio Doi¹

Abstract:
Tubulointerstitial nephritis (TIN) with IgM-positive plasma cells (IgMPC-TIN) is an autoimmune kidney disease characterized by IgM/CD138-double-positive plasma cell infiltration in the tubulointerstitium. A 50-year-old man developed IgMPC-TIN and presented with crystalline inclusions in the rough endoplasmic reticulum. Intracellular crystal formation is a rare finding in paraprotein-related kidney diseases, but this case showed no pathogenic monoclonal immunoglobulin. Prednisolone (PSL, 30 mg) improved the TIN, but PSL tapering resulted in the recurrence of TIN. Combination therapy with 15 mg PSL and 150 mg mizoribine ultimately stabilized TIN. This case offers original evidence concerning the pathophysiology and treatment strategy of IgMPC-TIN.

Key words: tubulointerstitial nephritis with IgM-positive plasma cells, intracellular crystalline inclusions in the rough endoplasmic reticulum, glucocorticoid dependence

(Intern Med Advance Publication) (DOI: 10.2169/internalmedicine.7118-21)

Introduction
Recently, tubulointerstitial nephritis (TIN) with IgM-positive plasma cells (IgMPC-TIN) has been proposed as a novel histological entity, and its clinical manifestations have been reported (1). IgMPC-TIN is presumed to be an autoimmune kidney disease that is characterized by several clinical and pathological features, such as a frequent occurrence in women, positivity for anti-mitochondrial antibodies, high serum IgM levels, IgM-positive plasma cell infiltration in the interstitium, and a good response to intermediate-dose glucocorticoids. IgMPC-TIN often occurs in patients with primary biliary cirrhosis/cholangitis (PBC), a chronic cholestatic liver disease. PBC is serologically characterized by positive anti-mitochondrial antibodies and high serum IgM levels. Immunohistochemical examinations have revealed IgM-positive plasma cell infiltration in the portal tract (2). Thus, we hypothesized that IgMPC-TIN might occur as a distinct kidney disease, independent of PBC, and that IgMPC-TIN and PBC might have a common pathological condition.

Since paraproteinemia can produce a spectrum of renal lesions, the pathophysiology of paraprotein-related kidney diseases has been clarified. A rare phenotype is intracellular immunoglobulin crystal formation (3, 4), which is associated with proximal tubular cells (5), interstitial histiocytes (6, 7), and podocytes (8, 9). The crystals are mostly made up of monoclonal κ light chains that are filtered through glomeruli and reabsorbed into each cell. In most cases, monoclonal κ
light chains belong to the Vκ1 variability subgroup, and most of them are encoded by the LC02/12 germ-line (10). These κ light chains frequently display an unusual hydrophobic residue at position 30 of the V domain (11). The peculiarities of the variable κ domain can account for the resistance to lysosomal proteolysis and promote self-aggregation and crystallization in lysosomes (12).

We herein report a man with glucocorticoid-dependent IgMPC-TIN who presented with uncommon findings of intracellular crystalline inclusions in the rough endoplasmic reticulum (rER).

### Case Report

A 50-year-old man was referred to our hospital for the evaluation of an elevated serum creatinine level of 1.44 mg/dL. This patient had a history of proteinuria and glycosuria for 10 years before the first visit. However, he had no contributory medical history, including neither hypertension nor diabetes mellitus, and was on no medication. He had a history of smoking (10 cigarettes/day for 30 years).

No abnormal physical findings were observed on a physical examination. Laboratory data are shown in Table 1. The patient’s urinalysis revealed a urine pH of 7.5, no hematuria, mild proteinuria of 0.31 g/day, glycosuria of 2.14 g/day, increased excretion of uric acid, elevated β2 microglobulin of 56,316 μg/L, and elevated L-type fatty acid-binding protein. A blood gas analysis revealed a pH of 7.361, a PCO2 of 31.1 mmHg, and an HCO3- concentration of 17.2 mEq/L, suggesting mild metabolic acidosis. These data imply tubular injury accompanied by renal tubular acidosis. Blood tests further revealed hypouricemia with 2.9 mg/dL, an elevated IgM level of 592 mg/dL, positivity for anti-nuclear antibodies, and elevated anti-mitochondrial antibodies at >160. These data indicated autoimmune tubulointerstitial nephritis. However, Sjögren syndrome, sarcoidosis, and IgG4-related kidney disease manifested by kidney involvement of tubulointerstitial nephritis were serologically excluded. Serum liver and biliary enzyme levels were within the normal range, and abdominal ultrasonography showed no hepatic abnormality, although anti-mitochondrial antibodies were specific to PBC.

A kidney biopsy was performed for a definitive diagnosis. Light microscopy revealed 13 glomeruli, 8 of which were globally sclerotic. The non-sclerotic glomeruli showed minor glomerular abnormality. Diffuse and moderate fibrosis, focal

### Table 1. Laboratory Test.

| (peripheral blood) | (chemical analysis) | (blood gas analysis) |
|-------------------|---------------------|----------------------|
| White blood cell 4.600 μL | Amylase 70 U/L | pH 7.361 |
| Neutrophil 71.5 % | Total cholesterol 170 mg/dL | pCO2 31.1 mmHg |
| Lymphocyte 17.5 % | HDL cholesterol 40 mg/dL | pO2 104.6 mmHg |
| Monocyte 6.5 % | Triglyceride 130 mg/dL | HCO3- 17.2 mEq/L |
| Eosinophil 3.5 % | Blood sugar 110 mg/dL | Anion gap 11.8 mEq/L |
| Red blood cell 341×10^6 /μL | HbA1c (NGSP) 5.2 % | (urinalysis) |
| Hemoglobin 16.4 g/dL | (serology) | |
| Platelet 19.5×10^6 /μL | C reactive protein 0.06 mg/dL | |
| AST 13 U/L | IgG 1.219 mg/dL | Protein 2+ |
| ALT 14 U/L | IgG4 55.9 mg/dL | Occult blood - |
| Lactate dehydrogenase 131 U/L | IgE 5.6 IU/mL | White blood cell - |
| γGTP 36 U/L | C3 74 mg/dL | (urine chemistry) |
| Alkaline phosphatase 285 U/L | C4 21 mg/dL | Protein 0.31 g/day |
| Total bilirubin 1.1 mg/dL | CH50 54 U/mL | Albumin 0.06 g/day |
| Total protein 7.6 g/dL | Rheumatoid factor 10 U/mL | Glucose 2.14 g/day |
| Albumin 4.4 g/dL | Anti nuclear antibody x160 | NAG 11.6 U/L |
| Uric acid 2.9 mg/dL | Anti mitochondrial Ab ×80 | β2microglobulin 56,316 μg/L |
| Blood urea nitrogen 20 mg/dL | Anti SS-A Ab (-) | L-FABP 67.9 μg/gCr |
| Creatinine 1.51 mg/dL | Anti SS-B Ab (-) | urine anion gap >0 mEq/L |
| Sodium 138 mEq/L | Serum monoclonal (-) | FEK 11.3 % |
| Potassium 4.1 mEq/L | protein (immunofixation) | FECA 3.2 % |
| Chloride 109 mEq/L | HbS Ag (-) | TmPGFR 2.55 mg/dL |
| Calcium 9.1 mg/dL | HCV Ab (-) | CUA/CCR 20.1 % |
| Phosphorus 2.7 mg/dL | | |
| Magnesium 2.2 mg/dL | | |

AST: aspartate transaminase, ALT: alanine aminotransferase, γGTP: γ-glutamyltransferase, Hbs Ag: hepatitis B surface antigen, HCV Ab: hepatitis C virus antibody, NAG: N-acetylgluosaminidase, L-FABP: liver-type fatty acid binding protein, FEK: fractional excretion of potassium, FECA: fractional excretion of calcium, TmPGFR: tubular phosphorus maximum resorption rate-to-glomerular filtration rate ratio, CUA/CCR: uric acid clearance-to-creatinine clearance ratio.
Figure 1. Light microscopic findings. Light microscopy showed the characteristic features of interstitial nephritis and tubulitis. Diffuse and moderate tubulointerstitial fibrosis (a, Masson Trichrome staining) and focal lymphocyte infiltration and tubular atrophy in the interstitium (b, Periodic acid-Schiff staining, ×200) were observed. Mononuclear lymphocytes had infiltrated between tubular epithelial cells (arrows in c, Hematoxylin and Eosin staining, ×400).

immunocyte infiltration and tubular atrophy in the tubulointerstitium were observed (Fig. 1a, b). Mononuclear lymphocytes infiltrated into tubules, thus suggesting tubulitis (Fig. 1c). No immune deposits were detected in the glomeruli or in the interstitium by routine immunofluorescence of fresh-frozen sections. Immunohistochemistry of formalin-fixed, paraffin-embedded specimens revealed inflammatory cell infiltration in the tubulointerstitium, where CD3-positive T cells were predominantly observed. CD138-positive plasma cells in the interstitium were mostly negative for IgG (Fig. 2). Dual immunostaining with IgM and CD138 using formalin-fixed, paraffin-embedded specimens after antigen retrieval was performed in the current case and in a control case (drug-induced TIN) (Fig. 3). IgM/CD138-dual positive plasma cell infiltration was clearly increased in this case compared with a control TIN case. Based on these findings, this patient was diagnosed with IgMPC-TIN.

Electron microscopy revealed club-shaped crystalline structures in the interstitium. At a higher magnification, the crystalline structures were shown to be surrounded by a dilated unit membrane that bounds to ribosomes, thus suggesting intracellular crystalline inclusions within the rER. The crystalline inclusions exhibited striated structures 6-7 nm in width with a center-to-center distance of 10-13 nm (Fig. 4). An abnormal mitochondrial morphology was not observed in the tubular epithelial cells.

The clinical course is shown in Fig. 5. Immunosuppressive therapy with 30 mg of prednisolone (PSL) was initiated. Urine protein, urine sugar, urine β2 microglobulin, serum IgM, and the estimated glomerular filtration rate (eGFR) were assessed as therapeutic markers. After PSL administration, the eGFR increased, concurrently with the improvement of IgM, urine β2 microglobulin, and urine sugar level. However, PSL tapering led to a decrease in the eGFR with worsening of findings for serum and urine markers. Thus, the intensification of therapy with a combined administration of 20 mg PSL and 75 mg cyclosporine A or 150 mg mizoribine was tested. This combination therapy was more effective than PSL monotherapy, although the decrease in PSL resulted in the deterioration of urine markers. Ultimately, 15 mg PSL with 150 mg mizoribine resulted in the stabilization of TIN, with normalized urine sugar and protein levels and low urine β2 microglobulin levels; the eGFR did not markedly deteriorate during the follow-up period.

Discussion

The characteristic pathological findings of IgMPC-TIN
are diffuse interstitial distribution of CD3-positive T lymphocytes and infiltrating IgM-positive plasma cells in the interstitium, as proven using dual immunostaining with CD138 and IgM (1). In particular, IgM-positive plasma cell infiltration is critical for a definitive diagnosis, as infiltration of IgG-positive plasma cells is a common finding in TIN (13). Therefore, in the present case, we revealed the co-expression of IgM (55199; CAPPEL, USA) and CD138 (M7228; DAKO, Denmark) on formalin-fixed, paraffin-embedded specimens after antigen retrieval (06380-05; Nacalai Tesque, Japan) using immunofluorescence. We confirmed that plasma cells were largely negative for IgM in control TIN specimens using the same method. In addition, we also observed similar results using immunohistochemistry with different anti-human IgM antibody (IR513; DAKO) (Supplementary File 1). We assumed that the epitopes of IgM expressed by immune deposits and plasma cells were different, so the detection of IgM expressed by plasma cells might require antigen retrieval process to clearly detect. Intriguingly, the current case showed crystalline inclusions.

Figure 2. Immunohistochemistry. Immunohistochemistry shows dominant CD3-positive T cell infiltration in the tubulointerstitium (a-d). CD138-positive plasma cells in the interstitium were largely negative for IgG (d and e). a-e show the same area in the cortex. Immunostaining was performed for formalin-fixed, paraffin-embedded specimens after antigen retrieval (a: CD3, b: CD20, c: CD68/PGM-1, d: CD138, e: IgG).

Figure 3. Dual immunostaining with IgM and CD138. Immunofluorescent staining revealed the infiltration of CD138-positive plasma cells labeled with IgM in the interstitium in the current case. The control case with drug-induced TIN showed the predominant infiltration of IgM-negative plasma cells. a/d: IgM, b/e: CD138, c/f: IgM/CD138/DAPI. DAPI, 4’,6-diamidino-2-phenylindole.
in the rER in interstitial cells. Immunoglobulins can accumulate intracellularly to form protein crystals under certain physiological conditions or disease settings. There are two types of intracellular immunoglobulin crystallization. One type occurs in the endosome/lysosome compartments, where phagocytosed or reabsorbed immunoglobulins traffic for recycling into circulation or for degradation. Crystallinclusions are formed during the catabolic process of immunoglobulins due to their resistance to lysosomal proteolysis. The other type of crystallization occurs in the rER, where immunoglobulin synthesis, folding, and assembly occur (14). To our knowledge, crystalline inclusion in the rER associated with kidney diseases has never been reported. However, 17 previous reports described crystalline inclusions in the rER in a variety of disease settings (Table 2) (15-31). Most of these were neoplastic and inflammatory diseases. Eight reports were associated with plasma cell dyscrasia. Six of 11 reports associated with lymphocytic cells described the detection of immunoglobulin-derived crystals. No particular subclasses of the heavy chain were detected in these reports; however, the light chain subclass was λ chain in four reports and κ chain in one report. These data suggest that lymphocytic cells actively producing immunoglobulins can form intra-rER crystals composed of heavy and light chains with peculiar physicochemical conditions.

The details of immunoglobulin crystal formation in the rER remain to be fully elucidated. Goldberg originally speculated that intracellular crystals were composed of structurally abnormal immunoglobulins that cells were unable to secrete (32). However, a recent in vitro study proposed that crystallization was the direct consequence of biosyntheticactivities in immunoglobulin-producing cells (33). CHO cells stably transfected with a full-length normal human IgG clone spontaneously induced the formation of rod-shaped crystals in the rER lumen. The intra-ER crystals were composed of reversibly soluble and correctly assembled and folded IgG. Likewise, intracellular crystal-derived IgG retained an antigen binding ability equivalent to that of secreted IgG. In addition, transiently transfected HEK293 cells developed intracellular crystals when ER export was blocked by brefeldin A. The authors concluded that export-ready IgG accumulated progressively in the ER lumen until a threshold concentration, necessary to nucleate the crystals, was reached. IgMPC-TIN is not plasma cell dyscrasia, but interstitial plasma cells were found to overproduce IgM in the current case. In addition, crystalline inclusions in our case showed striated structures that were 6-7 nm in width with a center-to-center distance of 10-13 nm.

Figure 4. Electron microscopic findings. Intracellular club-shaped crystalline inclusions were observed in interstitial cells (a. arrow). The arrowhead indicates the nucleus in b. The arrows show the membrane-bound ribosomes, suggesting that crystals were included in the distended rough endoplasmic reticulum (c). At a higher magnification, crystalline inclusions exhibited striated structures 6-7 nm in width with a center-to-center distance of 10-13 nm (d).
The optimal regimen of immunosuppressive therapy for IgMPC-TIN has not been determined, and the long-term renal prognosis is still unknown. However, we reported that patients with IgMPC-TIN receiving an intermediate dose of glucocorticoids often respond to the therapy, and their renal function was preserved at the last follow-up (0.2-15.0 years) (1). The current patient responded to 30 mg of glucocorticoids, with repeated recurrence after PSL tapering to less than 10 mg. We considered that urinary sugar, protein, and β2-microglobulin as well as serum IgM levels were useful biomarkers of disease activity. After the first recurrence, the combined administration of 20 mg of PSL with cyclosporine A or mizoribine was initiated. Combination therapy with glucocorticoids and immunosuppressants improved disease biomarkers more effectively than glucocorticoid monotherapy. In the follow-up period, 15 mg of PSL with 150 mg of mizoribine normalized urinary sugar and protein levels and improved urine β2-microglobulin levels despite slightly decreasing the eGFR in the follow-up period. PSL: prednisolone, CyA: cyclosporine A, MZR: mizoribine, eGFR: estimated glomerular filtration rate, Cr: creatinine

**Figure 5.** Clinical course. PSL (30 mg) alone increased the eGFR, accompanied by the improvement of IgM, β2-microglobulin, and urinary sugar levels; however, PSL tapering resulted in a decrease in the eGFR with worsening of serum and urine markers. Thus, the combined administration of 20 mg PSL and 75 mg cyclosporine A or 150 mg mizoribine was tested. The combination therapy was more effective than PSL monotherapy, although the decrease in PSL resulted in the deterioration of urine markers. Finally, 15 mg PSL with 150 mg mizoribine normalized urinary sugar and protein levels and improved urine β2-microglobulin levels despite slightly decreasing the eGFR in the follow-up period. PSL: prednisolone, CyA: cyclosporine A, MZR: mizoribine, eGFR: estimated glomerular filtration rate, Cr: creatinine

plasma cells that actively synthesized IgM. This is a rare cellular phenomenon in inflammatory kidney diseases.

The effect of combined therapy in IgMPC-TIN. A few cases of recurrent IgMPC-TIN have been reported. Matsuoka-Uchiyama et al. reported two cases of relapse after rapid tapering of glucocorticoids (36). Mizoguchi et al. reported a case of recurrent IgMPC-TIN associated with PBC after steroid tapering that improved following the administration of 500 mg of methylprednisolone per day for 3 consecutive days, followed by 10 mg of PSL daily (37). Further evidence will be required to determine the ideal regimen for improving the long-term prognosis in glucocorticoid-dependent IgMPC-TIN.

In conclusion, we encountered a man with recurrent IgMPC-TIN presenting with crystalline inclusions in the rER. This case may add further evidence to the pathophysiology and treatment strategy of IgMPC-TIN.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We would like to thank Editage (www.editage.jp) for the English language editing.
Table 2. Previous Reports Describing Crystalline Inclusions in Rough Endoplasmic Reticulum.

| author/year/Ref. | diagnosis                | organ                  | cell type or tissue          | origin of crystal            |
|------------------|--------------------------|------------------------|-----------------------------|------------------------------|
| Uzman/1971/#15   | hodgkin’s disease        | lymph node             | lymphoma cell               | undetermined                 |
| Clark/1973/#16   | chronic lymphocytic leukemia | peripheral blood  | leukemia cell               | IgMλ                         |
| Cawley/1973/#17  | chronic lymphocytic leukemia | peripheral blood  | leukemia cell               | IgAλ                         |
| Okawa/1975/#18   | multiple myeloma         | bone marrow            | myeloma cell                | undetermined                 |
| Johnson/1976/#19 | multiple sclerosis       | brain                  | astrocyte                   | undetermined                 |
| Rao/1980/#20     | papillary conjunctivitis | eye                    | plasmacytic lymphocyte      | IgG                          |
| Ralfkaier/1982/#21| chronic lymphocytic leukemia | peripheral blood  | leukemia cell               | IgMλ                         |
| Sun/1982/#22     | lymphoproliferative disorder | peripheral blood  | lymphocyte                  | undetermined                 |
| Flint/1984/#23   | malakoplakia             | stomach, submental region, oropharyngeal soft tissue | plasmacytoid cell | undetermined                 |
| Irro/1986/#24    | non-hodgkin lymphoma     | stomach                | lymphoma cell               | undetermined                 |
| Kobayashi/1987/#25| plasmacytoma             | stomach                | plasmacytoma cell           | IgMλ                         |
| Powell/1987/#26  | atrial myxoma            | heart                  | myeloma cell                | undetermined                 |
| Murray/1990/#27  | osteosarcoma             | bone                   | osteosarcoma cell           | undetermined                 |
| Drachenberg/1992/#28| HIV infection            | placenta               | syncytiotrophoblast         | human placental lactogen     |
| Bosman/1995/#29  | giant-cell fibroblastoma| nose                   | fibroblastoma cell          | vimentin                      |
| Seo/2002/#30     | adrenal cortical tumor   | adrenal gland          | adrenal tumor cell          | undetermined                 |
| Kobayashi/2007/#31| multiple myeloma         | bone marrow            | myeloma cell                | IgGκ                         |
| present case     | IgMPC-TIN                | kidney                 | undetermined                | undetermined                 |

HIV: human immunodeficiency virus, IgMPC-TIN: tubulointerstitial nephritis with IgMpositive plasma cells

Informed consent

Informed consent was obtained from all of the individual participants included in the study.

Ethical approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB approval number 680-1) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

References

1. Takahashi N, Saeki T, Komatsuda A, et al. Tubulointerstitial Nephritis with IgM-Positive Plasma Cells. J Am Soc Nephrol 28: 3688-3698, 2017.
2. Daniels JA, Torbenson M, Anders RA, Boitnott JK. Immunostaining of plasma cells in primary biliary cirrhosis. Am J Clin Pathol 131: 243-249, 2009.
3. Doshi M, Lahoti A, Danesh FR, Batuman V, Sanders PW. Paraprotein-Related Kidney Disease: Kidney Injury from Paraproteins-What Determines the Site of Injury? Clin J Am Soc Nephrol 11: 2288-2294, 2016.
4. Briodoux F, Leung N, Hutchison CA, et al. Diagnosis of monoclonal gammopathy of renal significance. Kidney Int 87: 698-711, 2015.
5. Stokes MB, Valeri AM, Herlitz L, et al. Light Chain Proximal Tubulopathy: Clinical and Pathologic Characteristics in the Modern Treatment Era. J Am Soc Nephrol 27: 1555-1565, 2016.
6. Stokes MB, Aronoff B, Siegel D, D’Agati VD. Dysproteinemia-related nephropathy associated with crystal-storing histiocytosis. Kidney Int 70: 597-602, 2006.
7. El Hamel C, Thierry A, Trouillas P, et al. Crystal-storing histiocytosis with renal Fanconi syndrome: pathological and molecular characteristics compared with classical myeloma-associated Fanconi syndrome. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 25: 2982-2990, 2010.
8. Matsuyama N, Joh K, Yamaguchi Y, et al. Crystalline Inclusions in the Glomerular Podocytes in a Patient With Benign Monoclonal Gammapathy and Focal Segmental Glomerulosclerosis. American Journal of Kidney Diseases 23: 859-865, 1994.
9. Nasr SH, Preddie DC, Markowitz GS, Appel GB, D’Agati VD. Multiple myeloma, nephrotic syndrome and crystalloid inclusions in podocytes. Kidney Int 69: 616-620, 2006.
10. Messiack T, Deret S, Mougenot B, et al. Adult Fanconi syndrome secondary to light chain gammapathy. Clinico-pathologic heterogeneity and unusual features in 11 patients. Medicine (Baltimore) 79: 135-154, 2000.
11. Aucoinlier P, Bauwens M, Khamlilchi AA, et al. Monoclonal Ig L chain and L chain V domain fragment crystallization in myeloma-associated Fanconi’s syndrome. J Immunol 150 (8 Pt 1): 3561-3568, 1993.
12. Leboulleux M, Lenolong B, Mougenot B, et al. Protease resistance and binding of Ig light chains in myeloma-associated tubulopathies. Kidney Int 48: 72-79, 1995.
13. Saeki T, Kawano M. IgG4-related kidney disease. Kidney Int 85: 251-257, 2014.
14. Hasegawa H. Aggregates, crystals, gels, and amyloids: intracellular and extracellular phenotypes at the crossroads of immunoglobulin physicochemical property and cell physiology. Int J Cell Biol 2013: 604867, 2013.
15. Uzman BG, Saito H, Kasae M. Tubular arrays in the endoplasmic reticulum in human tumor cells. Lab Invest 24: 492-498, 1971.
16. Clark C, Rydell RE, Kaplan ME. Frequent association of IgM lambda with crystalline inclusions in chronic lymphatic leukaemic lymphocytes. N Engl J Med 289: 113-117, 1973.
17. Cawley JC, Barker CR, Britchford RD, Smith JL. Intracellular IgA immunoglobulin crystals in chronic lymphocytic leukaemia. Clin
18. Oikawa K. Electron microscopic observation of inclusion bodies in plasma cells of multiple myeloma and Waldenström’s macroglobulinemia. Tohoku J Exp Med 117: 257-281, 1975.
19. Johnson T, Knobeloch L, Sunderland E, et al. Crystals, paracrystals, and rigid tubules in multiple sclerotic brain and spinal fluid. Lab Invest 35: 264-271, 1976.
20. Rao NA, Font RL. Plasmacytic conjunctivitis with crystalline inclusions. Immunohistochemical and ultrastructural studies. Arch Ophthalmol 98: 836-841, 1980.
21. Ralfkiaer E, Hou-Jensen K, Geisler C, Plesner T, Henschel A, Hansen MM. Cytoplasmic inclusions in lymphocytes of chronic lymphocytic leukemia. A report of 10 cases. Virchows Arch A Pathol Anat Histol 395: 227-236, 1982.
22. Sun CN, Amir J, White HJ. Crystalline inclusions within rough endoplasmic reticulum and perinuclear space of human lymphocytes. Cytologia (Tokyo) 47: 219-225, 1982.
23. Flint A, Murad TM. Malakoplakia and malakoplakialike lesions of the upper gastrointestinal tract. Ultrastruct Pathol 7 (2-3): 167-176, 1984.
24. Irro F, Gütz HJ, Mars G. [Signet-ring-cell lymphoma. Light and electron microscopic study of gastric involvement]. Arch Geschwulstforsch 56: 263-268, 1986 (in Ger).
25. Kobayashi Y, Miyake T, Funakoshi N, Kanoh T, Uchino H. Gastric plasmacytoma with cylindrical crystalline inclusions. Gastroenterol Jpn 22: 81-87, 1987.
26. Powell HC, Weissinger J. Intracysternal crystalline cytoplasmic inclusions in a cardiac myxoma. Am J Cardiovasc Pathol 1: 135-140, 1987.
27. Murray AB, Taccagni GL. Extraskeletal osteosarcoma with unusual ultrastructural features. Ultrastruct Pathol 14: 335-342, 1990.
28. Drachenberg CB, Papadimitriou JC. Endocrine secretory granules and crystals in the syncytiotrophoblast. J Submicrosc Cytol Pathol 24: 123-127, 1992.
29. Bosman C, Boldrini R, Pierro V, Corsi A. Unusual ultrastructural findings in giant-cell fibroblastoma. Tumori 81: 283-289, 1995.
30. Seo IS, Henley JD, Min KW. Peculiar cytoplasmic inclusions in oncocytic adrenal cortical tumors: an electron microscopic observation. Ultrastruct Pathol 26: 229-235, 2002.
31. Kobayashi C, Tanabe J, Aoki M, et al. [IgG-kappa type multiple myeloma with cytoplasmic crystalline inclusions]. Rinsho Ketsueki 48: 652-658, 2007 (in Jpn).
32. Goldberg AF. An unusual lymphomatous disease associated with intracytoplasmic crystals in lymphoplasmocytoid cells. Blood 16: 1693-1707, 1960.
33. Hasegawa H, Wendling J, He F, et al. In vivo crystallization of human IgG in the endoplasmic reticulum of engineered Chinese hamster ovary (CHO) cells. J Biol Chem 286: 19917-19931, 2011.
34. Ohtani H, Waki H, Komatsuda A, et al. Progressive glomerulopathy with unusual deposits of striated structures: a new disease entity? Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 25: 2016-2019, 2010.
35. Yamamoto T, Togawa A, Eguchi M, et al. Glomerulopathy with distinctive fibrillar deposits but lacking glomerular deposition of type III collagen. CEN case reports 5: 163-167, 2016.
36. Matsuoka-Uchiyama N, Tsuji K, Fukushima K, et al. Tubulointerstitial Nephritis Cases With IgM-Positive Plasma Cells. Kidney Int Rep 5: 1576-1580, 2020.
37. Mizoguchi S, Katayama K, Murata T, et al. IgM-Positive Tubulointerstitial Nephritis Associated With Asymptomatic Primary Biliary Cirrhosis. Kidney Int Rep 3: 1004-1009, 2018.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).