Significance of Intracytoplasmic Crystalline Inclusions in Plasma Cells – A Review with Case Discussion

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Abstract
Dense lymphoplasmacytic infiltrate in tissues pose diagnostic challenge to pathologists.

Presence of intracytoplasmic crystalline inclusions in plasma cells has been strongly linked with B-cell lymphoproliferative disorders, although isolated reactive cases are also reported. We reviewed the literature and present clinical, morphological and immunohistochemical findings in a polyp of the cervix. The polyp showed extensive plasma cell infiltrate with needle shaped and elongated intracytoplasmic inclusions in many of them. These cells were positive for CD 79a, CD 138, kappa and lambda light chain (equal proportions) and IgG. They were negative for cytokeratin, desmin, CD 20, CD 68, and IgA. Immunoprofile, laboratory data and clinical follow up were consistent with reactive nature of the lesion. This case highlights the fact that the presence of intracytoplasmic crystalline inclusions should not be considered pathognomonic of B-cell lymphoproliferative disorder.

Key words
Crystals, plasma cell, cervix.

Introduction
Lymphoid cells containing intracytoplasmic crystalline inclusions is an uncommon but well documented finding in B – cell lymphoproliferative disorders including plasmacytoma, multiple myeloma, chronic lymphocytic leukemia, lymphoplasmacytic lymphoma, mucosa- associated lymphoid tissue (MALT) lymphomas and rarely high grade lymphomas(1-5). However, some authors have noticed these crystals in reactive plasma cells infiltrate(1,6) but this is an extremely rare phenomenon and very few such cases have been reported(7,8,9,10) in the literature. To our knowledge intra-cytoplasmic crystalline inclusions in plasma cells have never been reported in female genital tract. We present morphological and immuno-histochemical findings in a 39 year old woman with a cervical polyp which showed extensive plasma cell infiltrate having intracytoplasmic elongated and needle shaped crystals. Pathogenesis is discussed. Clinical findings, laboratory results, and follow up is included with aim to highlight that crystals in plasma cells in isolation should not be considered diagnostic of lymphoproliferative disorder.

Case Report
A 39 year old lady, a mother of six children, presented to the gynaecology outpatient clinic complaining of dysparunia for 3 months duration. She had past history of uterovaginal prolapse, two years prior to the present complaint, which was surgically corrected. Pelvic examination (per speculum) revealed a polyp at the posterior cervical lip. Systemic examination was normal. Routine hematological and biochemical investigations were normal except for mild anemia (hemoglobin 10.5 g/L, total leukocyte count 7.3 x 10^9/L, differential leukocyte count N(58%) L(30%) M(7%) E(5%), platelet count 241 x 10^9/L, erythrocyte sedimentation rate 20 mm/h, blood glucose 4.9 mmol/L, urea 3.1 mmol/L, creatinine 49 µmol/L, bilirubin 2.4 µmol/L, total protein 69.2 g/L, sodium 137 mmol/L, potassium 4.3 mmol/L, and corrected calcium 2.12 mmol/L).

Following routine investigations polypectomy was performed. After identification of plasma cells with intracytoplasmic crystalline inclusions on histology, further work-up to exclude myeloma...
was done with serum and urine electrophoresis, urine for Bence Jones protein and skeletal survey. No monoclonal (M) band was noticed in serum or urine. Urine for Bence Jones protein was negative. Skeletal survey did not reveal any abnormality. Serum electrophoresis findings were as follows: albumin 39.32 g/L (normal 32 - 50 g/L), alpha 1 globulin 3.09 g/L (normal 1-4 g/L), alpha 2 globulin 6 g/L (normal 6 – 10 g/L), beta globulin 9.38 g/L (normal 6 – 13 g/L), gamma globulin 12.88 g/L (normal 7 – 15 g/L), IgG 12.3 g/L (normal 6.94 – 16.18 g/L), IgA 3.07 g/L (normal 0.65 – 3.78 g/L), IgM 1.94 g/L (normal 0.60 – 2.63 g/L).

Patient was kept under follow up. She is doing well after one and half year without any local or systemic complaint.

**Pathology**

Grossly, a polypoid grey white congested tissue piece measuring 1 x 0.8 x 0.3 was received in 10% neutral buffered formalin. Microscopically, the polyp was lined by benign endocervical and ectocervical epithelium with foci of ulceration. Subepithelium and stroma showed edema, capillary proliferation and mixed inflammatory cellular infiltrate consisting of numerous plasma cells, some neutrophils, lymphocytes and eosinophils (Figure 1). One third of the population of plasma cells was morphologically normal looking with eccentrically placed cart–wheel nuclei and perinuclear hoff. The rest of the plasma cells were oval to spindle shaped with eccentric nuclei and bright eosinophilic cytoplasm containing elongated and needle shaped crystalline inclusions (Fig 2 a&b). These plasma cells are referred to as plasma cells with crystals (PCC). The crystals were non–birefringent and were typically arranged in fan shaped parallel arrays. PCC mimicked rhabdomyoblasts focally and overall average count was 20/ HPF. Occasional plasma cells with cytoplasmic Russel bodies were also present but the inclusions were not observed in these cells. There were no histological features to suggest lymphoma. No histiocytes /macrophages containing crystals were identified.
Special histochemical stains i.e. periodic acid Schiff (PAS) with and without diastase, phosphotungstic acid hematoxylin (PTAH), and Gram’s stain along with battery of immunostains were done to confirm the nature of PCC. Immunostains comprised of cytokeratin (AE1 / AE3 clone); desmin; CD68; CD20; CD79α; kappa and lambda immunoglobulin light chain; and IgG, IgM and IgA heavy chains. PAS stain did not reveal any mucin or glycogen. PTAH was negative for cross striations. No microorganisms were noticed on PAS or Gram’s stain. Both morphologically normal looking plasma cells and PCC were negative for cytokeratin, desmin, CD20, CD68 & IgA. CD 79α and CD 138 showed surface and cytoplasmic positivity. IgG was positive in most of the cells and some cells showed IgM positivity. Lambda and kappa light chains stained the cytoplasm of plasma cells in equal proportions and interestingly they stained the cytoplasm of cells but fan shaped parallel arrays of crystals appeared as negative images (Figure 3).

Fig. 3: Immunostain for kappa light chain showing negative image of crystalline inclusions in PCC (DAB chromogen x1000).

Discussion

Intracellular and extracellular deposition of crystals is a rare phenomenon first described by Glauss in 1917(11). He described tumoral nodules that contained rod-like crystals in the ribs, vertebrae, sternum and long bones in multiple myeloma. Subsequently accumulation of intracytoplasmic crystalline inclusions has been described in various B-cell lymphoproliferative disorders specially in lymphomas showing plasmacytic differentiation.

The crystals have variable light microscopic appearances and may exhibit rectangular, elongated, needle shaped or rhomboid morphology. Electron microscopy typically reveals crystal localization within rough endoplasmic reticulum indicating that crystals represent synthesized but unreleased immunoglobulin. Furthermore demonstration of heavy chain and/or light chain immunoreactivity supports crystal origin from aggregated immunoglobulin components.

Immunoglobulin light chains produced by clonal B-cells may lead to an anomalous deposit in tissues which may be seen in different clinicopathological conditions(12, 13). First, AL-type amyloid is considered to be derived from variable portion of light chain and can be identified as Congo red positive homogenous substance. The second type of homogenous deposition is called systemic light-chain deposition disease. This deposition neither stains with Congo red nor does it show fibrillar arrangement of amyloid. The third type of deposition consists of crystals of light-chain derived proteins, often observed in tubules and glomeruli of kidney in patients with multiple myeloma(14, 15). The formation of crystals is thought to reflect altered production, storage or secretion of immunoglobulin products by the neoplastic cells and it seems likely that the abnormal proteins exhibit increased physicochemical tendency to crystallization. These inclusions may be immunoreactive for immunoglobulin components, typically there is weak or absent staining. This lack of immunoreactivity may be due to the altered molecular configuration and therefore decreased antigenicity of stored immunoglobulin or antigen masking due to crystalline structure of protein(3, 4) and special technique such as immunoelectron microscopy may be required to demonstrate specific labeling(16). Although the crystals usually accumulate within plasma cells, they can also be seen in extracellular locations or within phagocytic histiocytes. In the latter condition (crystal-storing histiocytosis), the histiocytic component predominate and may mask the underlying lymphoproliferative disorder(7, 17).
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Formation of intracytoplasmic crystals has been linked so much to lymphoproliferative disorders that some authors have suggested that identification of plasma cells can be used to support a diagnosis of lymphoproliferative disorder \(^{(1)}\). Only few case reports are available in literature where PCC were found in reactive conditions. Few cases of gastritis \(^{(9, 10)}\), and a case of osteoarthritis \(^{(8)}\) are reported. PCC have never been reported in female genital tract to our knowledge. This case demonstrated extensive plasma cell infiltrate in a cervical polyp. Both PCC and normal looking plasma cells were identified. PCC contained elongated and needle shaped crystals as described in previous case reports with reactive conditions \(^{(8, 9, 10)}\). Plasma cells containing Russel bodies were also noticed in the present case but these cells did not contain the intracytoplasmic inclusions. Histiocytes containing crystals \(^{(7, 17, 19)}\) and PCC associated with microorganisms \(^{(9, 10)}\) as noted by some authors were not observed. We assessed the PCC with battery of immunostains. CD 79 \(\alpha\) and CD1 positivity with negative staining for CK and desmin confirmed the plasma cells. Findings of IgG positivity in most of them and equal proportion of lambda and Kappa light chains in the cytoplasm of PCC was in keeping with previous case report of osteoarthritis \(^{(8)}\) and indicated the chronic reactive nature of the plasma cells. There were no histological features to suggest neoplasia. Furthermore, no paraprotein was detected in serum or urine electrophoresis, skeletal survey was normal, and clinical follow up is negative. Since the PCC showed negative images of needle shaped crystals, we feel that the plasma cells contain immunoglobulins with altered structural and molecular properties affecting their antigenecity.

**Conclusion**

We describe first case of intracytoplasmic crystalline inclusions in reactive plasma cells in female genital tract. In view of histomorphology, laboratory data and clinical follow-up we highlight the fact that crystalline intracytoplasmic inclusions can be seen in reactive conditions and should not be considered pathognomonic of B-cell lymphoproliferative disorder.

**References**


