Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL12, ISSUE 06, 2021

Systematic Review

Inclusion bodies: A systematic review

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Abstract
Inclusion Bodies Inclusion bodies are dense, spherical, aggregated proteins, mostly formed in the cytoplasm of prokaryotes due to overexpression of heterologous proteins. A detailed description of the formation of inclusion bodies is reported elsewhere. Inclusion bodies reflect light and so can be visualized by phase-contrast microscopy. At high expression level, inclusion bodies may occupy about 40-50% of the total cell proteins. This research paper is an attempt to review various types of inclusion bodies in a systematic manner.
Keywords: Inclusion bodies, protein, negri bodies, viral infections

Introduction
Inclusion bodies or elementary bodies are nuclear or cytoplasmic aggregates of stable substance. Inclusion bodies usually contain very little protein, ribosomal component of DNA/RNA fragments. Identification of inclusion bodies has become a useful diagnostic tool for certain viral infections.[1] Virus-induced aggregates play a dual role in virus propagation in the infected cells. The recruitment of host cellular proteins into cytoplasmic and nuclear inclusions to facilitate virus replication has been described for many viruses. Inclusion bodies are dense electron-refractile particles of aggregated protein found in both the cytoplasmic and periplasmic spaces of *E. coli* during high-level expression of heterologous protein. It is generally assumed that high level expression of non-native protein (higher than 2% of cellular protein) and highly hydrophobic protein is more prone to lead to accumulation as inclusion bodies in *E. coli*. [2, 3]. Inclusion bodies have a non-unit lipid membrane. Protein inclusion bodies are classically thought to contain misfolded protein. However, this has recently been contested, as green fluorescent protein will sometimes fluoresce in inclusion bodies, which indicates some resemblance of the native structure and researchers have recovered folded protein from inclusion bodies [4]. The classification of inclusion bodies is given below [5, 6, 7].
It is named for William Henry Howell and Justin Howell-Jolly bodies are histopathological findings of basophilic nuclear remnants (clusters of DNA) in circulating erythrocytes. During maturation the bone marrow erythrocytes normally expel their nuclei but in some cases a small portion of DNA remains. Nuclear fragments in the erythroid precursors are probably due to disordered nucleic acid synthesis resulting from vitamin B12 or folic acid deficiency. Similar inclusions are also found in cases of iron anaemia. Howell-Jolly bodies are not refractile, a feature that distinguishes them from artefacts. Since occasional Howell Jolly bodies occur in normal marrows and in conditions in which deficiency of B12 or folic acid can be excluded, less than 1% of Howell-Jolly bodies has no signifi etiology such as anaemia but more than this number or the presence of multiple bodies in one cell can be appreciated but not pathognomonic of vitamin B12 or folic acid deficiency. The fourth stage in the developmental series is that of polychromatophilic megaloblasts. In which asynchromism between nucleus and protoplasm is seen, which manifest a big nucleus in conjunction with a small cytoplasm or a small nucleus in conjunction with a large cytoplasm. The cytoplasm shows vivid colours, purple or greenish with heterogeneous areas of variable shapes. The nucleus still has a partly reticulated structure and may undergo mitotic division or fragmentation which produces an aspect of a petalled flower. The nucleus is still young as shown by its tra pearl-like aspect. But the tendency toward the formation of fragments of the nucleus classifies the cell as an old type of cell. The nuclear fragments appearing early in the cell are the future jolly's bodies (Jacques mallarmé, 1948).

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Table 1: Classification of inclusion bodies found in various diseases [4, 5]

S. No.	Type
1.	**Viral Inclusion Bodies** **Intracytoplasmic eosinophilic** a. Negri bodies in Rabies (Figure 1). b. Guarnieri bodies in vaccinia, variola. c. Paschen bodies in variola or small pox. d. Bollinger bodies in fowlpox. e. Henderson-Patterson bodies in Molluscum contagiosum. **Intranuclear eosinophilic** a. Cowdry type A in Herpes simplex virus and Varicella zoster virus. (Figure 2). b. Torres bodies in Yellow fever. c. Cowdry type B in Polio and adenovirus. **Intranuclear basophilic** a. Cowdry type B in Adenovirus. b. "Owl's eye appearance" in cytomegalovirus (Figure 3). **Mixed (both intranuclear and intracytoplasmic)** a. Warthin-Finkeldey bodies in Measles.
2.	**Inclusion bodies in RBCs** **Developmental organelles** **Howell-jolly bodies:** Small, round fragments of the nucleus resulting from karyorrhexis or nuclear disintegration of the late reticulocyte and stain reddish-blue with Wright stain. (Figure 4) **Basophilic stipplings**: These stipplings are either fine or coarse, deep blue to purple staining inclusion that appears in erythrocytes on a dried Wright stain. (Figure 5) **Pappenheimer bodies:** Are siderotic granules which are small, irregular, dark-staining granules that appear near the periphery of a young erythrocyte in a Wright stain. **Polychromatophilic red cells:** Young red cells that no longer have nucleus but still contain some RNA. **Cabot Rings:** Ring-like structure and may appear in erythrocytes in megaloblastic anemia or in severe anemias, lead poisoning and in dyserythropoiesis, in which erythrocytes are destroyed before being released from the bone marrow. (Figure 6) **Abnormal hemoglobin precipitation** **Heinz bodies:** Round bodies, refractile inclusions not visible on a Wright stain film. It is best identified by supravital staining with basic dyes. **Hemoglobin H Inclusions:** Alpha Thalassemia, greenish-blue inclusion bodies appear in many erythrocytes after four drops of blood is incubated with 0.5mL of Brilliant cresyl blue for 20 minutes at 37 °C. **Protozoan Inclusion** a. Malaria b. Babesia
3.	**Inclusion bodies in bacteria** Polyhydroxyalkanoates or PHA are produced by bacteria as inclusion bodies, the size of PHA granules are limited in *E. coli.*
4.	**Pseudo-inclusions** Pseudo-inclusions are invaginations of the cytoplasm into the cell nuclei, which may give the appearance of intranuclear inclusions. They may appear in papillary thyroid carcinoma.

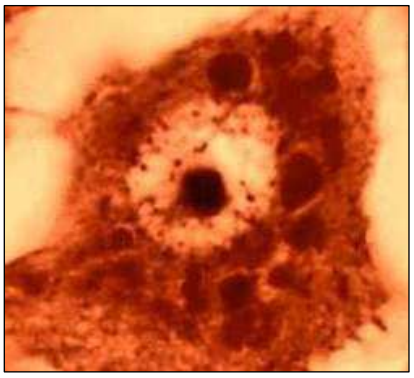

Fig 1: Negri body in rabies

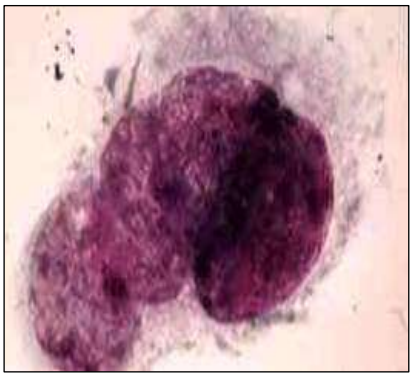

Fig 2: Lipschutz body of herpes zoster, vesicle of lip (Giemsa stain Tzank prepertion)

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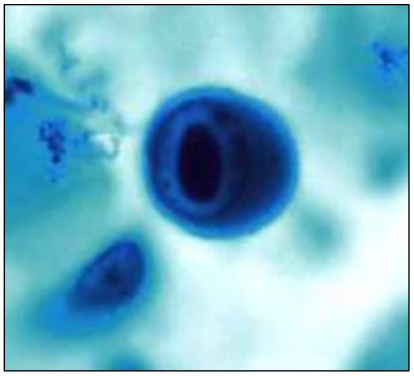

Fig 3: Cytomegalovirus (CMV) inclusion body, including an ntranuclear inclusion with surrounding halo (papanicolaou staining X20)

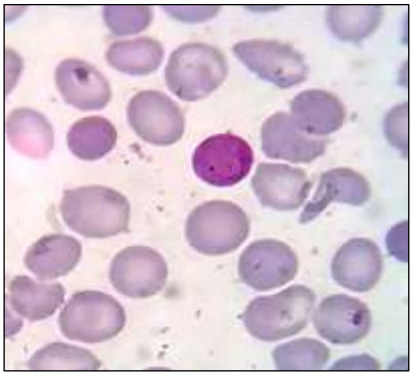

Fig 4: Cabot ring in a patient with megaloblastic anemia

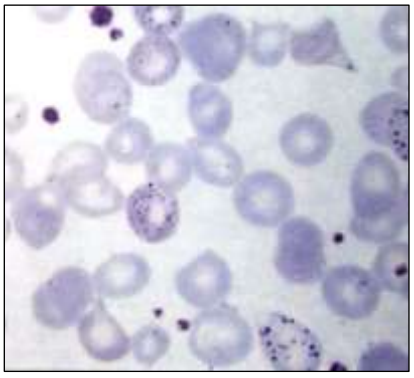

Fig 5: Basophilic stippling in a patient with lead poisoning

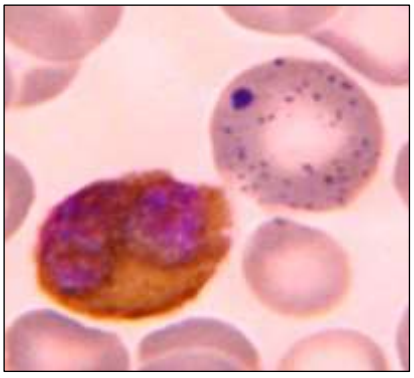

Fig 6: Howell Jolly body in a patient with megaloblastic anemia

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