

J Oral Maxillofac Pathol. 2013 May-Aug; 17(2): 154–155.

PMCID: PMC3830218

doi: [10.4103/0973-029X.119737](https://doi.org/10.4103/0973-029X.119737)

## ORPHAN ANNIE-EYE NUCLEI

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The nucleus forms the central part of a cell which controls gene expression and mediates the replication of deoxyribonucleic acid (DNA) during cell cycle. Two main types of nuclei which we usually encounter are the open face (transcriptionally active cells), consisting of large areas of euchromatin and the closed faced nucleus (transcriptionally inactive cells-most of its genome is in inactive state) with heterochromatin areas. There are various other forms of nuclei which exhibit significant and interesting morphological features. Here, we would like to discuss a not so rare, but a unique entity–Orphan Annie-eye nuclei.

The hand drawn illustration of Orphan Annie-eye nuclei, reveals large nuclei cleared out in the center with powdery chromatin marginated to the periphery along with few open- and close-faced nuclei [[Figure 1](#)].

Photomicrograph showing numerous Orphan Annie-eye nuclei with few hyperchromatic and vesicular nuclei [[Figure 2](#)].

The term was coined by Dr. Nancy E. Warner (Professor of Pathology at University of Southern California, USA) upon noticing tumor cells with empty nuclei or those showing just a thin rim of peripheral chromatin in sections of papillary thyroid carcinoma. The appearance of these abnormal nuclei to Dr. Nancy Warner, resembled the “Eyes Of Orphan Annie”. Little Orphan Annie was a daily comic strip created by American cartoonist Harold Gray which was quite popular in the period of 1894-1968.[[1](#)]

Its first official appearance in the context of pathology was in her book, Basic Endocrine Pathology in 1971. It was quoted as; “The epithelium may betray its malignant nature by a nuclear pattern; the nuclei have sharply etched membranes and instead of hyperchromatism, the center of nucleus is relatively empty (like Orphan Annie eyes)”.[[1,2](#)]

Features of Orphan Annie-eye nuclei in histopathology include, large nuclei, oval/molded with singular membranes, nuclear clearing with powdery chromatin, nuclear grooves, one/more marginally placed micro nucleoli, nuclear crowding with optically clear ground glass appearance, and nuclei that are often seen overlapping on each other.[[3,4](#)]

These are also referred to as “ground glass ground” as it appears to be cleared out from the center with most of its chromatin marginated onto the inside of the nuclear membrane, while the center of the nucleus stains faintly appearing as a hollow or washed out area.[[1,5](#)]

The nuclear changes in Orphan Annie-eye nuclei is divided into two major categories. The pathogenesis of

which is uncertain and may/may not be related to each other.

- The clearing itself is thought to be due to the disappearance/fine dispersion (hypoploidia)/displacement of chromatin resulting in a vesicular appearance of the nucleus
- A number of morphologic alterations of the nuclear membrane such as increased synthesis of nuclear membrane which then folds into itself leading to semilunar nuclear forms with a finely serrated contour, longitudinal grooves, and pseudo inclusions are also considered.[6]

Orphan Annie-eye nuclei are characteristically seen in

- Papillary thyroid carcinoma
- Polymorphous low grade adenocarcinoma
- Cribriform adenocarcinoma of tongue
- Autoimmune thyroiditis: Hashimoto's disease, Grave's disease, and nodular goiter.

Somatic rearrangements of the RET (rearranged during transfection) proto-oncogene are the most frequent genetic abnormality found in papillary thyroid carcinoma. Studies have shown that transfecting thyroid cells with RET oncogene may be the cause of this specific nuclear change in papillary thyroid carcinoma. However, the role of RET proto-oncogene in tumor progression still needs to be defined.

Although little Orphan Annie's eyes may not appear in comic strips in future, but we can see them appearing in histopathology for years to come as a useful diagnostic feature in various pathologies, especially so in salivary gland pathology.

## ACKNOWLEDGEMENT

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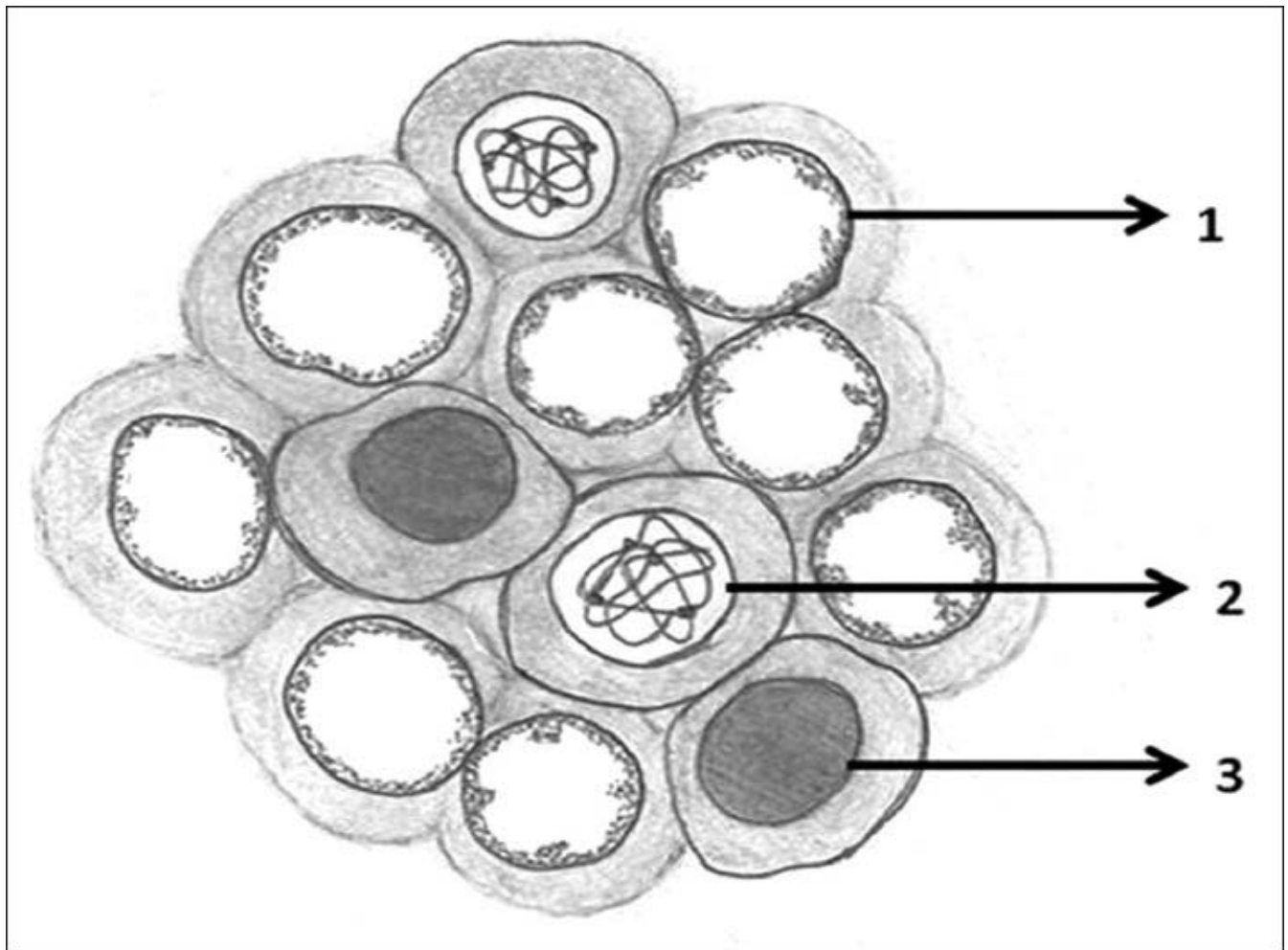
## FOOTNOTES

**Source of Support:** Nil.

**Conflict of Interest:** None declared.

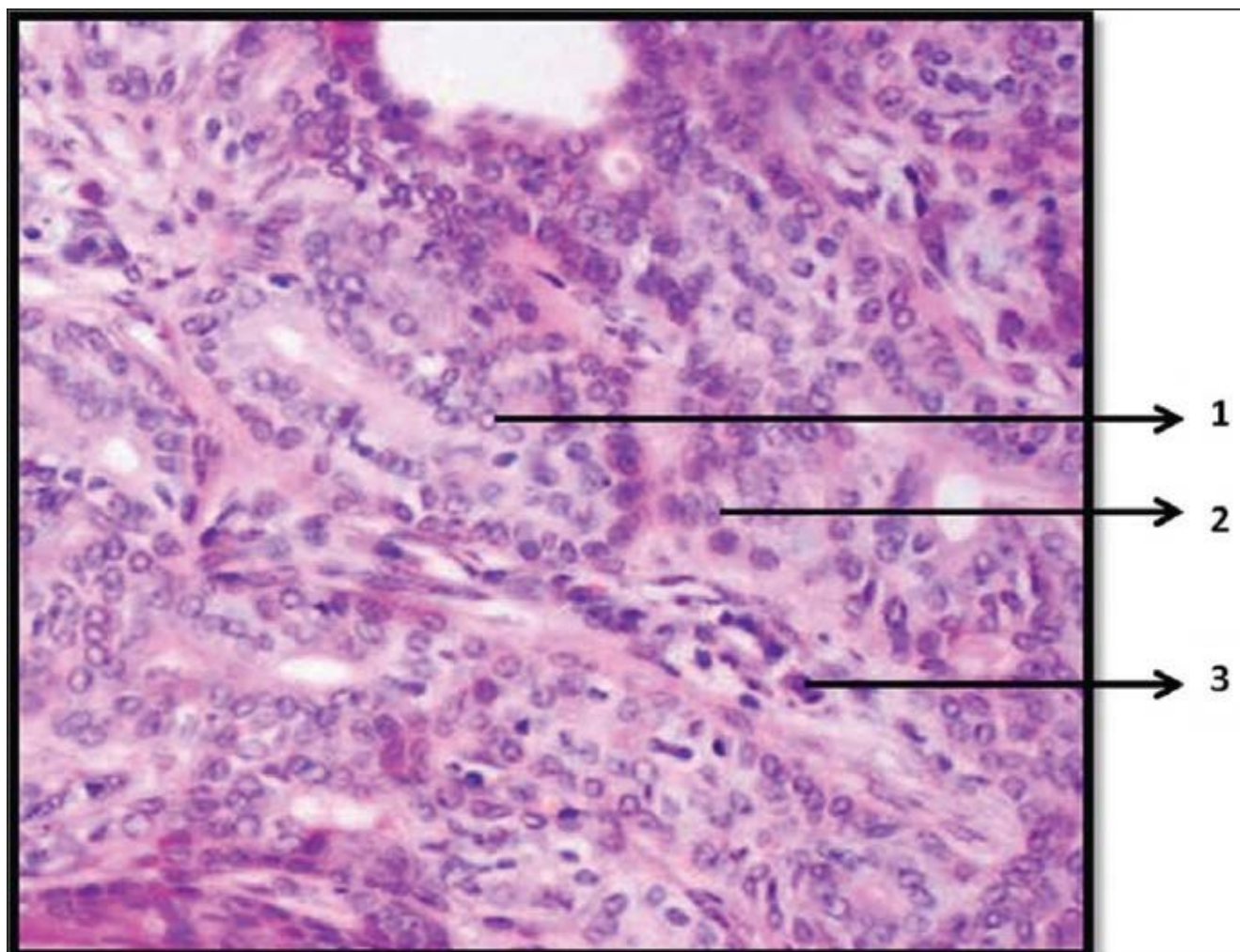
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**FIGURES AND TABLES****Figure 1**

The hand drawn illustration of Orphan Annie-eye nuclei reveals large nuclei cleared out in the center with powdery chromatin margined to the periphery along with few open- and close-faced nuclei. 1=Orphan Annie-eye nuclei, 2=open-faced nuclei, 3=closed-faced nuclei)

**Figure 2**



Photomicrograph showing numerous Orphan Annie-eye nuclei with few hyperchromatic and vesicular nuclei. 1=Orphan Annie-eye nuclei, 2=open-faced nuclei, 3=closed-faced nuclei (H & E,  $\times 200$ )

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