Introduction to cancer genetic susceptibility syndromes

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Introduction

- Cancer genetic susceptibility syndromes, including those that predispose to leukemia and lymphoma, have been increasingly identified during recent years.

- associated germ line mutations

- Cancer is at its root a genetic disease resulting from the accumulation of mutations that deregulate cellular differentiation, proliferation, and/or survival.

- In the majority of human cancers, these mutations are believed to occur in a single postzygotic cell.

- Nonetheless, the existence of cancer-prone kindreds has suggested that some of human cancers have a hereditary basis.

- This possibility was first recognized in 1866, Paul Broca reported a large kindred with multiple members affected with breast cancer.

- In the decades, many other cancer-predisposing genes more than 100 different genes and associated syndromes identified including:

- Rb 1 hereditary cancer retinoblastoma
- NF1 in neurofibromatosis type 1 (NF1),
- APC in familial adenomatous polyposis (FAP)
- TP53 in LFS
- BRCA1 and BRCA2 in hereditary breast–ovarian cancer.

- The majority of cancer susceptibility genes encode tumor suppressors, proteins that restrain cell growth by inhibiting cell cycle progression.

- mutations in these genes impair normal growth control, and thus increase the risk for cancer.

Genetic susceptibility syndromes that predispose to hematopoietic cancers

- Leukemias and lymphomas are seen in association with a number of cancer genetic susceptibility syndromes.

- it is estimated that about 2% to 4% of patients with hematopoietic malignancies develop the disease as a result of an underlying predisposition

- Such is the case in conditions characterized by defects in DNA repair (Fanconi anemia [FA], ataxia telangiectasia, constitutional mismatch repair deficiency [CMMRD], LFS)

- signal transduction (NF1, Noonan syndrome)

- lymphocyte development (Wiskott Aldrich syndrome).

leukemia or lymphoma may be the primary oncologic manifestation of a genetic condition:

- familial acute lymphoblastic leukemia (ALL)

a result of germ line mutations in ETV6- and PAX5

- Acute myeloid leukemia (AML) as a result of germ line mutations in RUNX1, CEBPA, or GATA

- disorders associated with development of lymphoma, such as X-linked lymphoproliferative disease.

Factors to consider when evaluating for a cancer genetic susceptibility syndrome

- When assessing a patient or family with hematopoietic cancers for the presence of an underlying cancer susceptibility syndrome

3 key domains to consider:

- including the family cancer history
- presenting features of the tumor and histology
- physical examination or cognitive/developmental manifestations.

- Hematologists/oncologists should consider each of these domains and refer to a cancer genetics specialist when there is a suspicion of an underlying syndrome

Family cancer history

- The presence of a positive family cancer history is one of the strongest and most well accepted indicators of an underlying cancer genetic susceptibility syndrome.

- It is recommended that the family history be taken at the first clinic visit and involve collection of data from at least first- and second-degree relatives.

Ideally, the family history should include:

- collection of data on the type of cancer in relatives
- age at cancer diagnosis
- relative is from the maternal or paternal lineage.

- Environmental exposures
- details of cancer treatment
- history of excessive toxicity to cancer treatment
- prophylactic surgical procedures to reduce cancer risk (colectomy, mastectomy, or hysterectomy) should also be noted

- When considering a leukemia or lymphoma predisposition syndrome
- First, it is important to assess 1 or more relatives developed a hematopoietic malignancy

- to determine the lineage (lymphoid vs myeloid) (non-Hodgkin's vs Hodgkin's) and (acute vs chronic).

- individuals with leukemia developed the disease as a primary or therapy-related neoplasm

- lymphoma, it is important to ask whether the cancer occurred in the setting of an immunodeficiency or in association with Epstein-Barr virus (EBV) infection.

other manifestations:

- such as a history of antecedent anemia, leukopenia, thrombocytopenia, or the presence of growth or developmental delays and congenital anomalies.

- Each of these pieces of data can facilitate identification of the relevant leukemia or lymphoma predisposition syndrome or syndromes, and thus guide subsequent genetic counseling and testing.

- Although most syndromes follow an autosomal dominant inheritance, alternative genetic mechanisms (autosomal recessive, polygenic)

- lifestyles or environmental exposures, may explain certain familial cancer cases.

Features of solid tumors that are suggestive of an underlying syndrome:

- include bilateral involvement of paired organs
- multifocal tumors
- multiple primary tumors.

- Specific solid tumor types should prompt consideration of a genetics evaluation even in the absence of a positive family history.

- include adrenocortical or choroid plexus carcinomas, which are caused by germ line TP53 mutations in a high proportion of cases.

- Similarly, certain cytogenetic, genetic and other features of cancer, including a hematopoietic malignancy predisposition syndrome.

- Up to 50% of children with hypodiploid ALL germ line TP53 mutations.
- up to 72% with MDS and monosomy 7 carry germ line GATA2 mutations.

- CEPBA mutation in 7% to 11% of cases familial AML
- RUNX1 mutations could herald AML.
- Finally, B-cell non-Hodgkin lymphomas occurring in association with EBV should prompt consideration of an immunodeficiency disorder.

- Consistent with these data, a study of breast cancer survivors with therapy-related leukemia identified germ line mutations in BRCA1, BRCA2, TP53, CHEK2, and PALB2 that collectively accounted for 21% of cases.

Physical features

- Many cancer genetic susceptibility syndromes are associated with nononcologic manifestations include:

- physical findings
- cognitive or developmental delays
- presence of certain benign tumors.

- For many of these conditions, it is important to note that the “defining” manifestations may precede a cancer diagnosis by several years.

- Thus, clinicians should be attuned to the possible presence of these features and refer patients to a cancer genetics specialist once they are identified

Dermatologic manifestations.

- The skin is often affected in cancer predisposition syndromes
- One of the most common dermatologic manifestations is the cafe au lait macule
- can be seen in several cancer genetic syndromes, including those that predispose to hematopoietic cancers (NF1, Noonan syndrome, FA).

- Other benign skin findings include freckl in the inguinal/axillary region (NF1)

- mucocutaneous hyperpigmentation (Peutz-Jeghers syndrome)
- eczema (WAS)
- telangiectasias (ataxia telangiectasia)

- Dermatologic cancers seen in predisposition syndromes include:

- squamous cell carcinoma (FA)

- melanoma (familial multiple mole melanoma syndrome, hereditary breast–ovarian cancer, LFS)

- basal cell carcinoma (Gorlin syndrome, LFS).

Developmental anomalies.

- The etiologies of developmental delay, autism disorder, and intellectual disabilities are vast and often unknown.

- However, the occurrence of these manifestations in a patient with MDS or hematopoietic malignancy warrants further evaluation

Congenital anomalies and other physical features.

- The presence of 1 or more congenital anomalies or other atypical physical features may also serve as an important clue for underlying cancer predisposition.

- For instance, differences in growth patterns such as short stature and/or microcephaly may suggest conditions associated with DNA repair, such as FA, Bloom, Nijmegen breakage

- Sensorineural hearing loss can occur in familial MDS/AML caused by germ line GATA2 or SRP72 mutations.

- Primary lymphedema also can occur in individuals with GATA2 mutations.

- Hair and nail abnormalities are seen in individuals with dyskeratosis congenita.

- Finally, skeletal anomalies are features of several cancer genetic syndromes, including FA, Shwachman-Diamond syndrome, and Diamond-Blackfan anemia.

Incorporation of germ line genetic information into clinical practice

- knowledge of the phenotypes associated with specific cancer susceptibility syndromes has improved
- ability to test for these conditions
- use genetic information to guide clinical management.
- patients suspected of having a cancer genetic susceptibility syndrome should be referred to a professional with training in cancer genetics.

- There are many potential benefits, both for the patient with cancer and his or her family, of making a diagnosis of an underlying cancer genetic susceptibility syndrome.

- For example, in some mutation carriers, certain chemotherapeutic agents may be dose-modified, organ-sparing surgical approaches may be indicated, radiation therapy may be reduced or even eliminated, or allogeneic stem cell transplantation (allo-SCT) should be considered.

- For patients with bone marrow failure, MDS, or leukemia, therapeutic choices may be informed by the presence of a predisposing mutation.

- For example, patients with hereditary bone marrow failure syndromes or MDS generally do not achieve sustained remission with immune suppression.

- As a result, these patients should be treated with allo-SCT.

- Finally, it is important to screen relatives for the presence of a known familial mutation to exclude those who have the mutation from being a stem cell donor.

- Patients with underlying cancer genetic susceptibility syndromes also become candidates for tumor surveillance.
- Surveillance is most suited for patients with solid tumors, where outcomes are more often linked to the initial stage of the tumor at diagnosis.
- In theory, solid tumors identified through surveillance may be smaller and require treatment with less-invasive surgical procedures, and possibly less or no chemotherapy or radiation therapy

- when to start, when to stop, intervals between surveillance tests.

- Surveillance is also complicated by the possibility of false-positive test results, which lead to increased anxiety, as well as increased follow-up imaging and invasive procedures.

- Finally, there are many unanswered questions related to the cost-benefit ratio of surveillance and whether the early detection of tumors really leads to significant enhancements in long-term outcomes.

- At present, consensus guidelines regarding the optimal methods of surveillance for individuals with hematopoietic cancer-predisposing genetic syndromes are lacking.

- Some recommend that individuals undergo a baseline bone marrow aspirate and biopsy to assess for occult malignancy
- regular physical examinations
- complete blood cell counts with differential

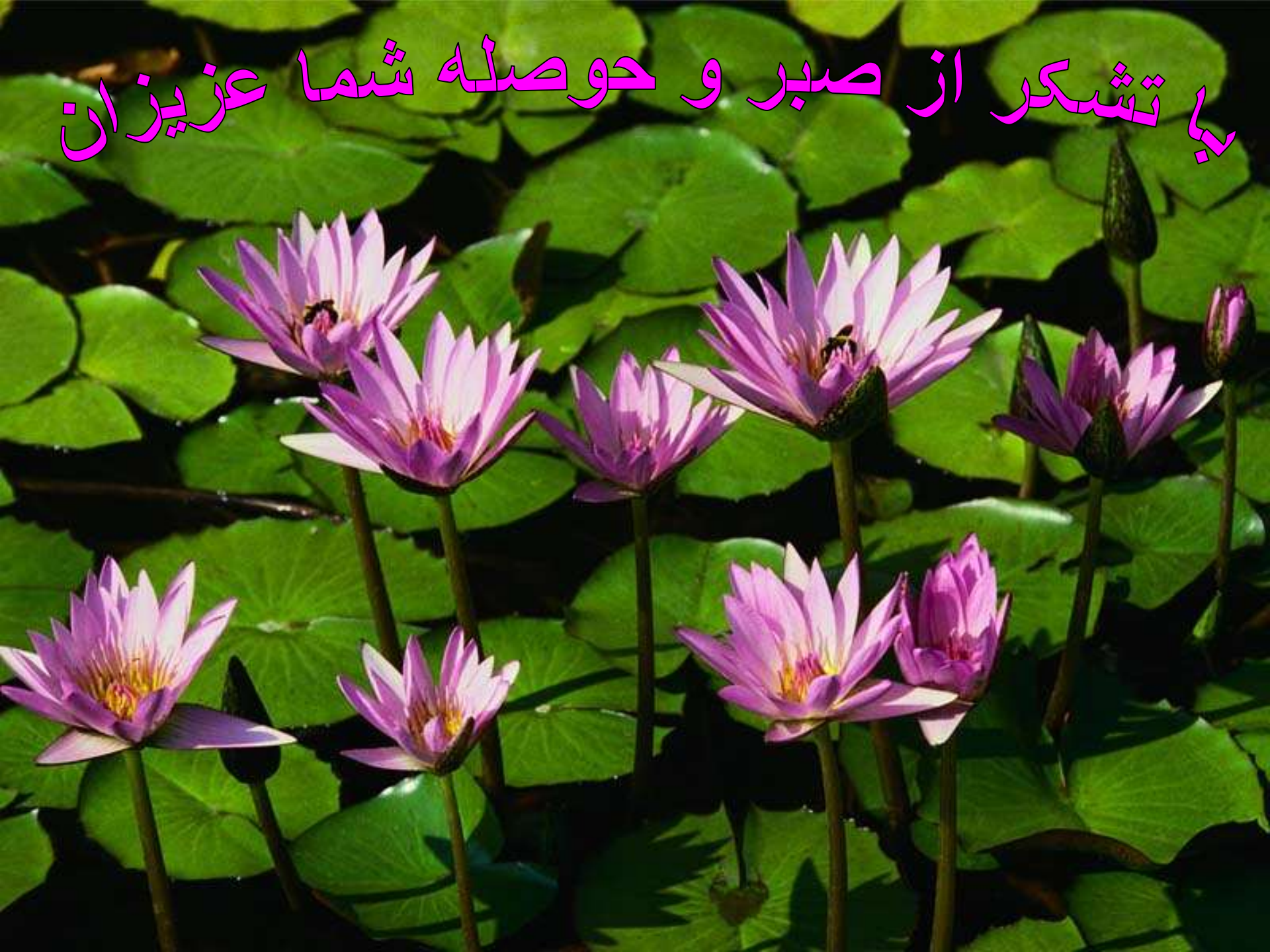
Conclusions

- When faced with the diagnosis of cancer, patients and relatives will invariably question its cause.

- As we are learning, an increasing proportion of cancers are caused by an underlying genetic susceptibility.

- Although many questions remain unanswered
- it is anticipated that ongoing and future discoveries will further increase knowledge of the host genetic factors that influence cancer risk
- development of more effective cancer treatments, surveillance protocols, and risk-reducing measures.

- For some cancer genetic susceptibility syndromes, identification of at-risk individuals allows for cancer preventive measures, primarily prophylactic surgeries that can reduce or even eliminate the chances of developing cancer.
- Multiple endocrine neoplasia type 2 and FAP and breast cancer are excellent examples, in which early removal of the thyroid or colon or breast respectively, can prevent the development of cancer.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