Miscellaneous

Hong Kong College of Radiologists
MC 1 Pyrexia of unknown origin

1. Pyrexia of unknown origin
2. Clinical history, physical examination, laboratory tests, CXR
3. Specific diagnosis established?
   - Yes
     - Order appropriate investigations
   - No
     - Further investigations based on initial laboratory results and discussion with radiologists
8. Suspected DVT of lower extremities
   - Yes
     - Doppler US of lower limb veins
     - Positive
       - Proper management +/- follow-up
     - Negative
       - Contrast-enhanced CT abdomen and pelvis (+/- thorax)
           - No established diagnosis
           - After discussion with radiologists / nuclear medicine physicians
               - F-18 FDG PET-CT scan
                 - Alternative: Gallium scan or WBC scan
               - No established diagnosis
                 - Further workup / follow-up / proper management
           - Diagnosis established
             - Proper management +/- tissue diagnosis +/- follow-up
   - No

9. Proper management +/- follow-up
MC 1 Pyrexia of unknown origin

REMARKS

1 General
   1.1 Definition of pyrexia of unknown origin
      1.1.1 Pyrexia of unknown origin was first defined as an illness of greater than 3
            weeks’ duration with a temperature higher than 101°F (38.3°C) on several
            occasions and an uncertain diagnosis after 1 week of study in the hospital.
      1.1.2 The requirement of 1 week in-patient evaluation has been recently modified
            and only evaluation of 3 out-patient visits or 3 days of in-hospital evaluation
            are stated in some articles.2,4
   1.2 Classifications based on patient’s subtypes include: classic, nosocomial, immune
            deficient and human immunodeficiency virus (HIV) associated, which may require
            different investigations pathway.2,3
      1.2.1 The classic pyrexia of unknown origin excludes patients with known
            immunodeficiency or HIV infection.2
   1.3 Causes of pyrexia of unknown origin3,5
      1.3.1 Infectious, oncologic, inflammatory and miscellaneous/unknown are the four
            main categories.
      1.3.2 There is an increasing trend of pyrexia of unknown origin in which the cause
            remains unknown.4,6,7
      1.3.3 Infection is the most common cause. However, many factors may affect
            the implementation of study results to clinical practice due to different
            geographic locations, different subgroups of patients and different types of
            institutions.3

2 Radiography
   2.1 Some articles have listed out the minimum diagnostic evaluation to qualify as pyrexia
            of unknown origin. Chest X-ray (CXR) is among one of the first investigations.6,8

3 The decision to obtain any further diagnostic studies should be based on abnormalities
   found in the initial laboratory work-up.3 Further diagnostic studies should be performed
   after discussion with radiologists/nuclear medicine physicians.

4 CT
   4.1 For further diagnostic workup, CT of the abdomen should be one of the first
            investigations since it has a high diagnostic yield, with reported yield rate being
            19%.6,9
   4.2 No definite evidence to support CT thorax for evaluation of pyrexia of unknown
            origin. Consideration of the investigation should be based on patient’s clinical
            history, physical examination, laboratory test and initial chest radiographic findings.

5 Nuclear Medicine
   5.1 Gallium scan and white blood cell (WBC) scan
      5.1.1 Conventional scintigraphic methods are Ga-67 citrate scintigraphy, In-111
            labeled or Tc-99m labeled WBC scintigraphy. These techniques have their
            disadvantages and limitations, such as handling of potentially infected blood
            products (labeled WBC scintigraphy), and the relatively long time span
            between injection and diagnosis.14
5.2 F-18 FDG PET-CT

5.2.1 Compared with conventional scintigraphy, advantages of FDG PET-CT include higher resolution, higher sensitivity in chronic low-grade infections, higher accuracy in the central skeleton, as well as shorter time period between injection of the radiopharmaceutical and the imaging procedure. Furthermore, FDG shows an increased vascular uptake in patients with vasculitis.¹⁴

5.2.2 Beside, FDG is accumulated in various types of malignancy, which can be a cause of pyrexia of unknown origin.

6 US

6.1 Venous thrombosis is a cause of prolonged fever. Studies revealed that it is a cause of pyrexia of unknown origin in 2-6%.⁵,¹³ Although deep vein thrombosis (DVT) accounts for a small percentage of pyrexia of unknown origin, Doppler US is a safe method to identify the treatable cause.⁶
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REFERENCES

Metastasis from unknown primary

Clinical history, physical examination, laboratory tests, CXR

Suspicious site identified?

Yes → Order appropriate investigations

No → Further investigations based on initial assessment and discussion with radiologists

Cervical LN metastases

Yes → Contrast CT of the head and neck +/- MRI of the head and neck

Primary identified → Proper management +/- tissue diagnosis +/- follow-up

No primary identified → Consider Proper management +/- tissue diagnosis +/- follow-up

Isolated axillary LN metastases in females (adenocarcinoma)

Yes → Mammography +/- ultrasound of breast +/- breast MRI

Primary identified → Proper management +/- tissue diagnosis +/- follow-up

No primary identified → Consider Proper management +/- tissue diagnosis +/- follow-up

Suspicious site identified?

Yes → Order appropriate investigations

No → Further investigations based on initial assessment and discussion with radiologists

Contrast-enhanced CT thorax, abdomen and pelvis ( +/- neck)

No primary identified → After discussion with radiologists / nuclear medicine physicians

Whole body PET-CT

Primary identified → Proper management +/- tissue diagnosis +/- follow-up

No primary identified → Consider Proper management +/- tissue diagnosis +/- follow-up
REMARKS

1 General
1.1 ‘Cancer of unknown primary’ refers to a condition in which a patient has metastatic malignancy without an identified primary source, which is a very heterogeneous disease.1
1.1.1 Different terms have been used to differentiate patients at different stages of investigative pathway1
1.1.1.1 ‘Malignancy of undefined primary origin’—metastatic malignancy identified on the basis of a limited number of tests, without an obvious primary site, before comprehensive investigation
1.1.1.2 ‘Provisional carcinoma of unknown primary’—metastatic epithelial or neuroendocrine malignancy identified on the basis of histology/cytology, with no primary site detected despite a selected initial screen of investigations, before specialist review and possible further specialized investigations
1.1.1.3 ‘Confirmed carcinoma of unknown primary’—metastatic epithelial or neuroendocrine malignancy identified on the basis of final histology, with no primary site detected despite a selected initial screen of investigations, specialist review and further specialized investigations as appropriate
1.2 Incidence is about 3-5% of all cancers registered in the United Kingdom.1,2
1.3 Chest X-ray (CXR) and CT scan of the chest, abdomen and pelvis are among the initial radiological investigations offered to patients with malignancy of undefined primary origin, depending on patient’s symptoms.1,3

2 Radiography
2.1 Lung Cancer is the most common cause of metastasis from unknown primary.2,4 CXR is a cheap and very rapidly performed test to detect lung cancer.2

3 CT
3.1 CT of the thorax, abdomen and pelvis with the use of intravenous contrast material is a useful initial investigation.1,2,3,5,6
3.2 The recommendation of CT thorax is also based on its better detection of lung cancer than CXR.5,7
3.3 Contrast-enhanced CT of the head and neck is also useful for identification of primary tumour in patients with cervical lymph node metastases from unknown head and neck primary cancers.8,9,10

4 Breast Imaging
4.1 Do not routinely offer mammography to women with metastasis from unknown primary unless clinical or pathological features are compatible with breast cancer.1
4.2 Breast MRI should be considered in women presenting with isolated axillary adenopathy which is adenocarcinoma on histology and suspicious of breast primary, after negative initial mammography and ultrasonography.1,2,3
MRI
  5.1 MRI has superior soft tissue contrast for head and neck imaging.\textsuperscript{8,11}

PET scan
  6.1 Whole-body Fluorodeoxyglucose (FDG) PET-CT may contribute to the management of patients with cervical adenopathies from occult primary and those with a single metastasis from occult primary. For other cases of metastases from occult primary, the role of FDG PET-CT is limited.\textsuperscript{13}
  6.2 FDG PET-CT is not recommended in routine systematic work-up for all cases of metastasis from occult primary.\textsuperscript{13,14}
  6.3 FDG PET-CT may be warranted in cases considered for local or regional therapy.\textsuperscript{14}

Image-guided biopsy
  7.1 It is recommended that needle core biopsy or surgical biopsy should be obtained for histological assessment for evaluation of metastasis from unknown primary.\textsuperscript{1,2}
REFERENCES

2. Taylor MB, Bromham NR, Arnold SE. Carcinoma of unknown primary: key radiological issues from the recent National institute for health and clinical excellence guidelines. BJR. 2012; 85: 661-671.