BOLESTI LIMFOCITA I PLAZMA STANICA

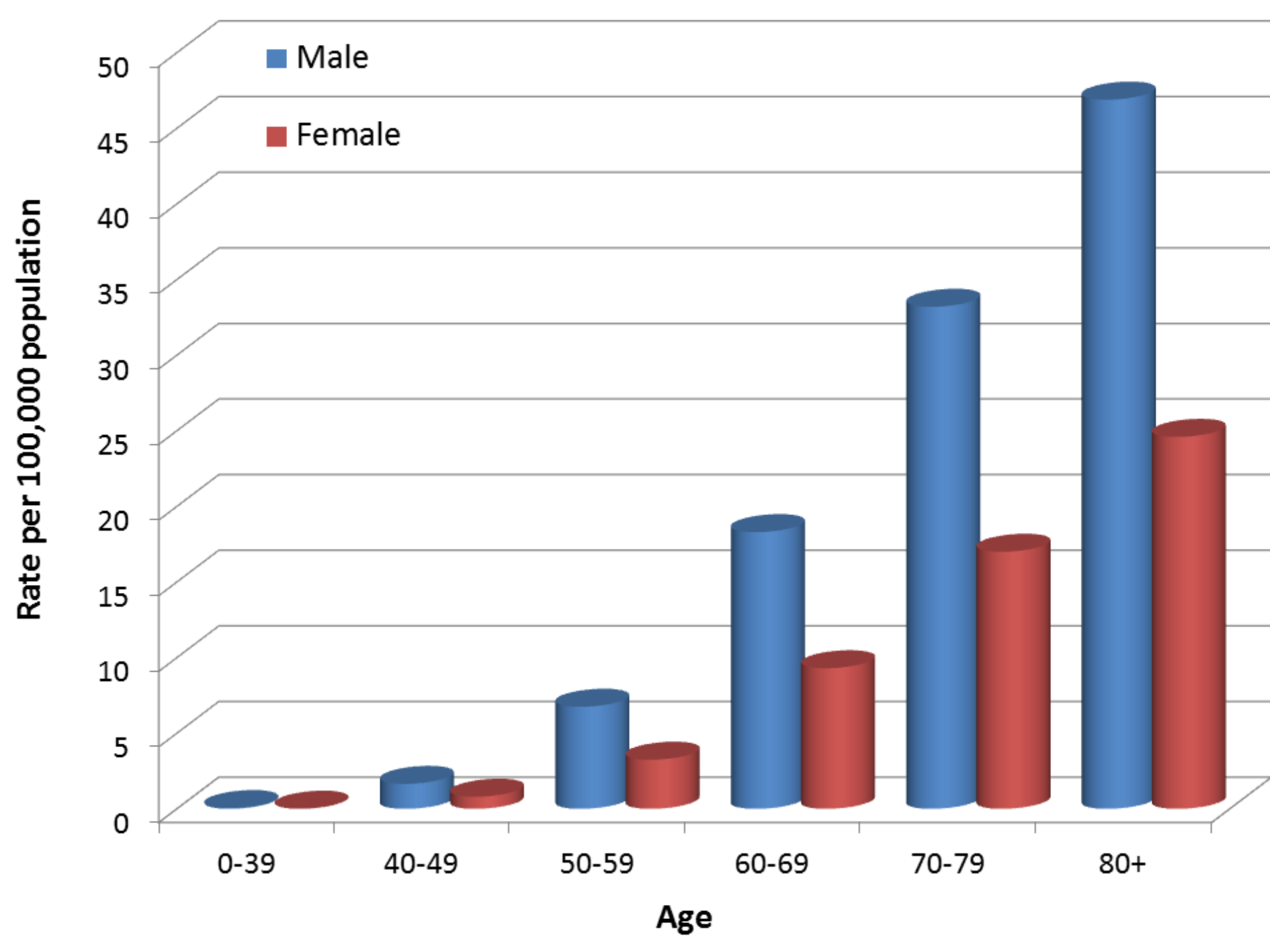
Petar Gaćina

BOLESTI LIMFOCITA

- Akutna limfoblastična leukemija
- Kronične limfocitne leukemije:
  - B kronična limfocitna leukemija
  - Prolimfocitna leukemija
  - Leukemija vlasastih stanica
  - Kronična leukemija diferenciranih T limfocita
- Zloćudni limfomi: ne-Hodgkinovi limfomi
  - Hodgkinov limfom

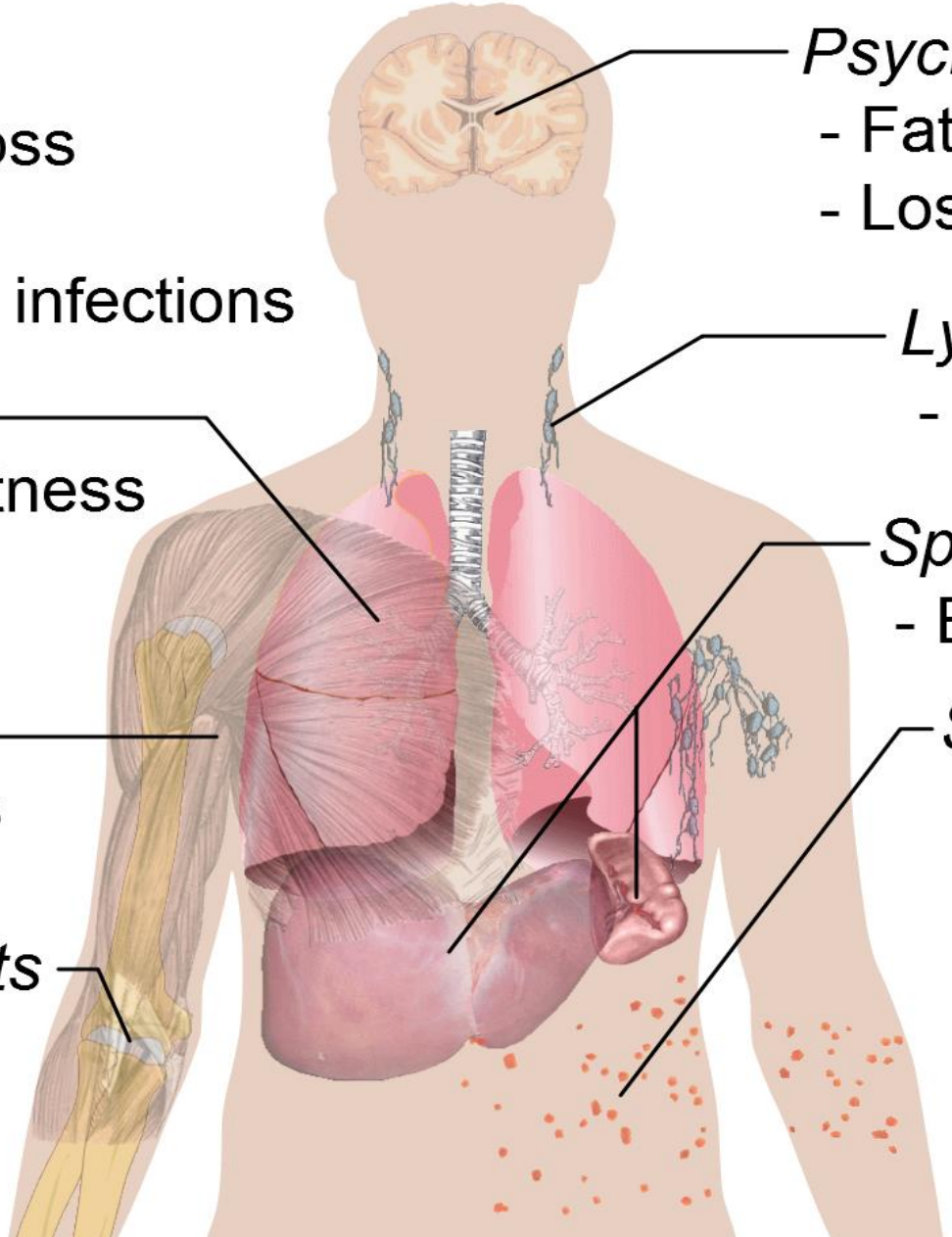
B- kronična limfocitna leukemija

- Najčešća vrsta leukemija u odraslih osoba (20-30% svih leukemija)
- Nastaje klonalnim bujanjem CD5+ B limfocita
- M:Ž=2:1
- Nepoznata etiologija
- Genetski čimbenici ?


Male
Female
50
45
40
35
30
25
20
15
10
5
0
Rate per 100,000 population
0-39
40-49
50-59
60-69
70-79
80+
Age

Common symptoms of

Leukemia



Systemic
- Weight loss
- Fever
- Frequent infections

Psychological
- Fatigue
- Loss of appetite

Lymph nodes
- Swelling

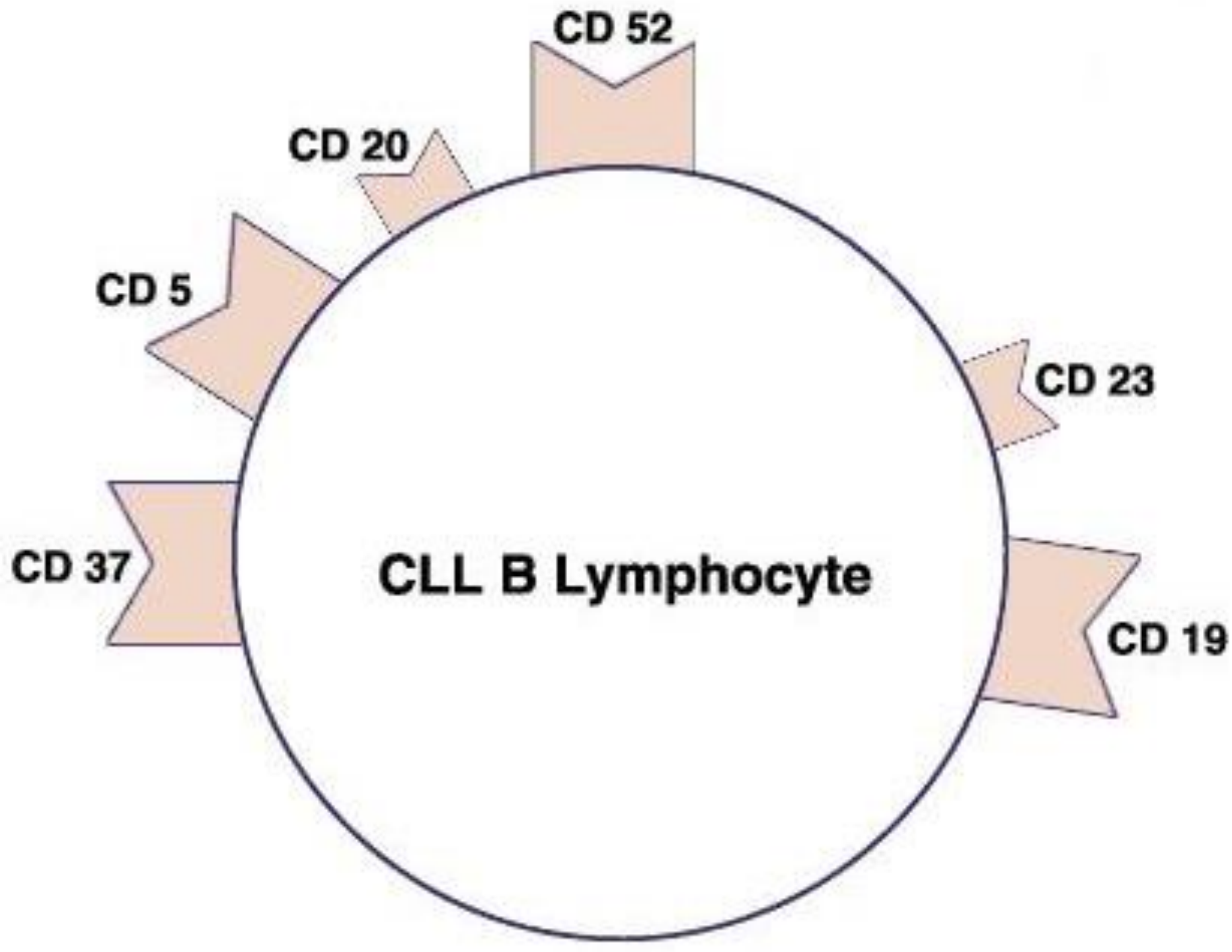
Lungs
- Easy shortness of breath

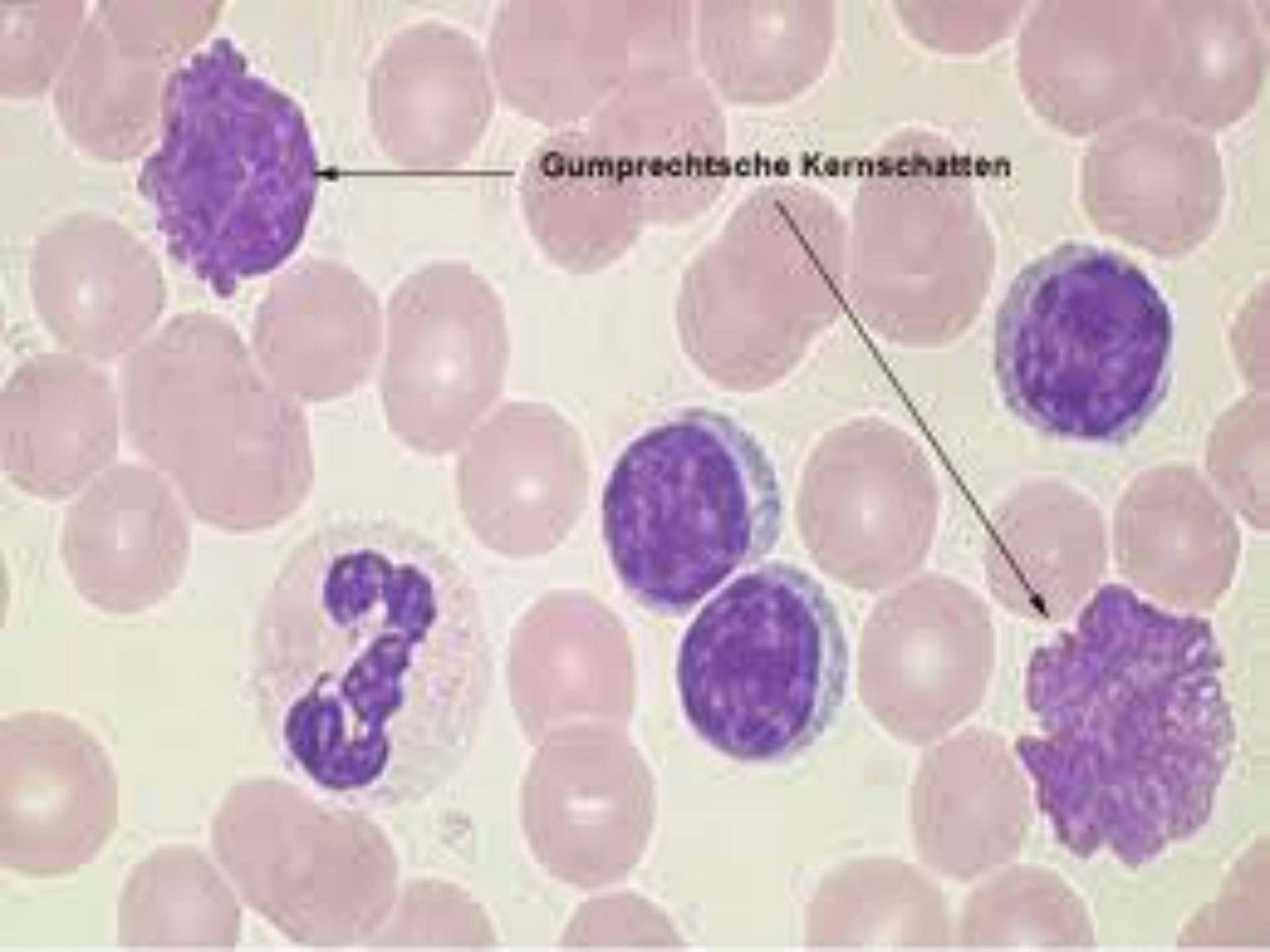
Spleen and/or liver
- Enlargement

Muscular
- Weakness

Skin
- Night sweats
- Easy bleeding and bruising
- Purplish patches or spots

Bones or joints
- Pain or tenderness


CD 52
CD 20
CD 5
CD 23
CD 37
CLL B Lymphocyte
CD 19


Gumprechtsche Kernschatten

B- kronična limfocitna leukemija

- LIJEČENJE

- Antileukemijsko (klorambucil, fludarabin, rituksimab, CVP protokol)
- Potporno (suzbijanje hematoloških, imunoloških i metaboličkih komplikacija)

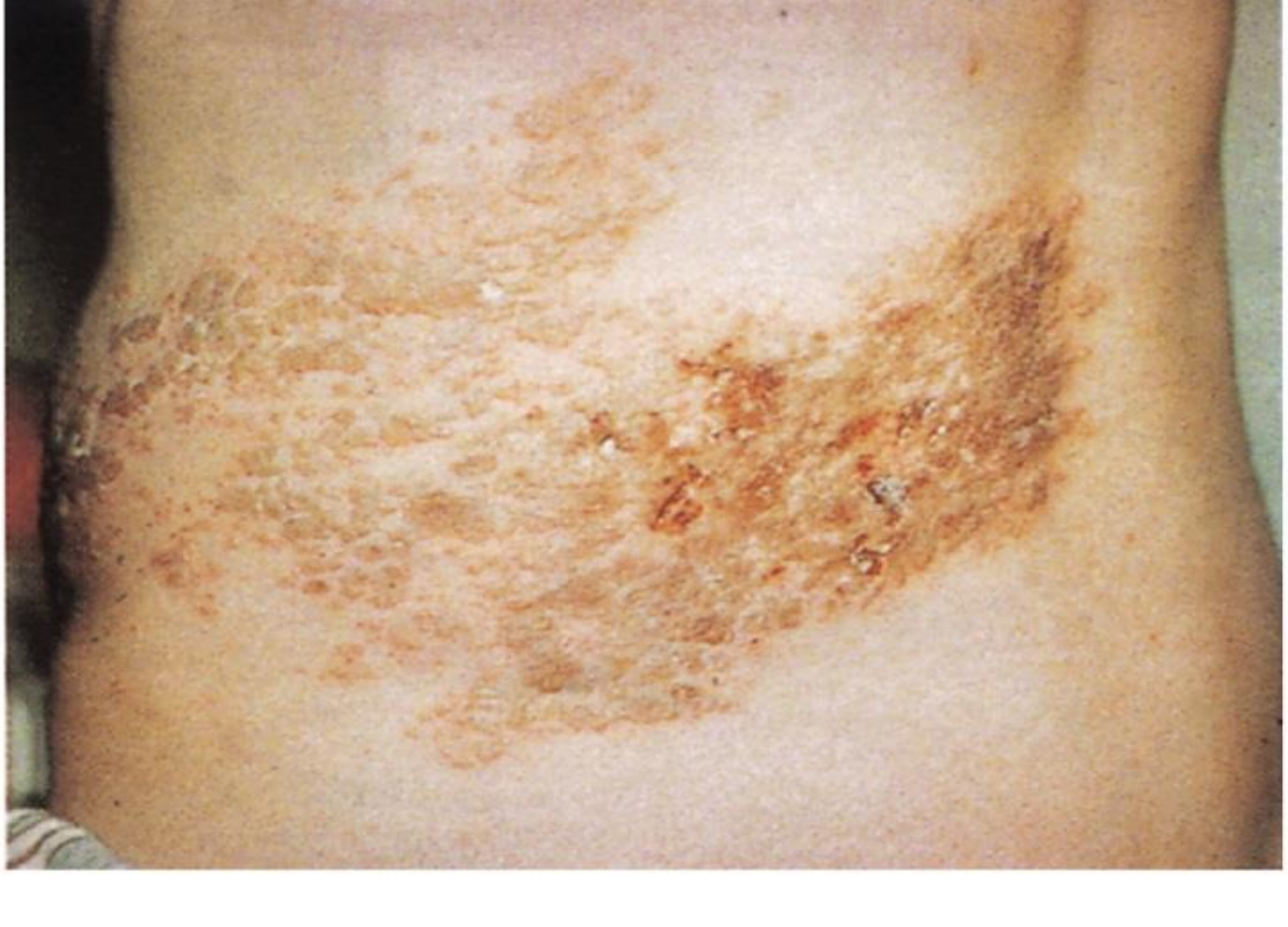


Figure 18.2 Chronic lymphocytic leukaemia: herpes zoster infection in a 68-year-old female.

Hoffbrand's Essential Haematology, Seventh Edition. By A. Victor Hoffbrand and Paul A. H. Moss. Published 2016 by John Wiley & Sons Ltd.

B- kronična limfocitna leukemija

- Preživljenje vrlo različito, od nekoliko mjeseci do više od 10, pa i 20 godina (prosječno 5-6 godina)
- Česti uzroci smrti su infekcije (41%), preobrazba u druge zloćudne bolesti
- Oko 30% bolesnika umire od bolesti nevezano za leukemiju (najčešće srčanožilnih)

Ne-Hodgkinovi limfomi

DEFINICIJA:

Heterogena skupina limfoproliferativnih npl. Karakterizirana pojavom maligno promijenjenih limfocita u limfnim čvorovima, a rijeđe primarno u drugim organima.

- Najčešće očitovanje je bezbolno povećanje limfnog čvora

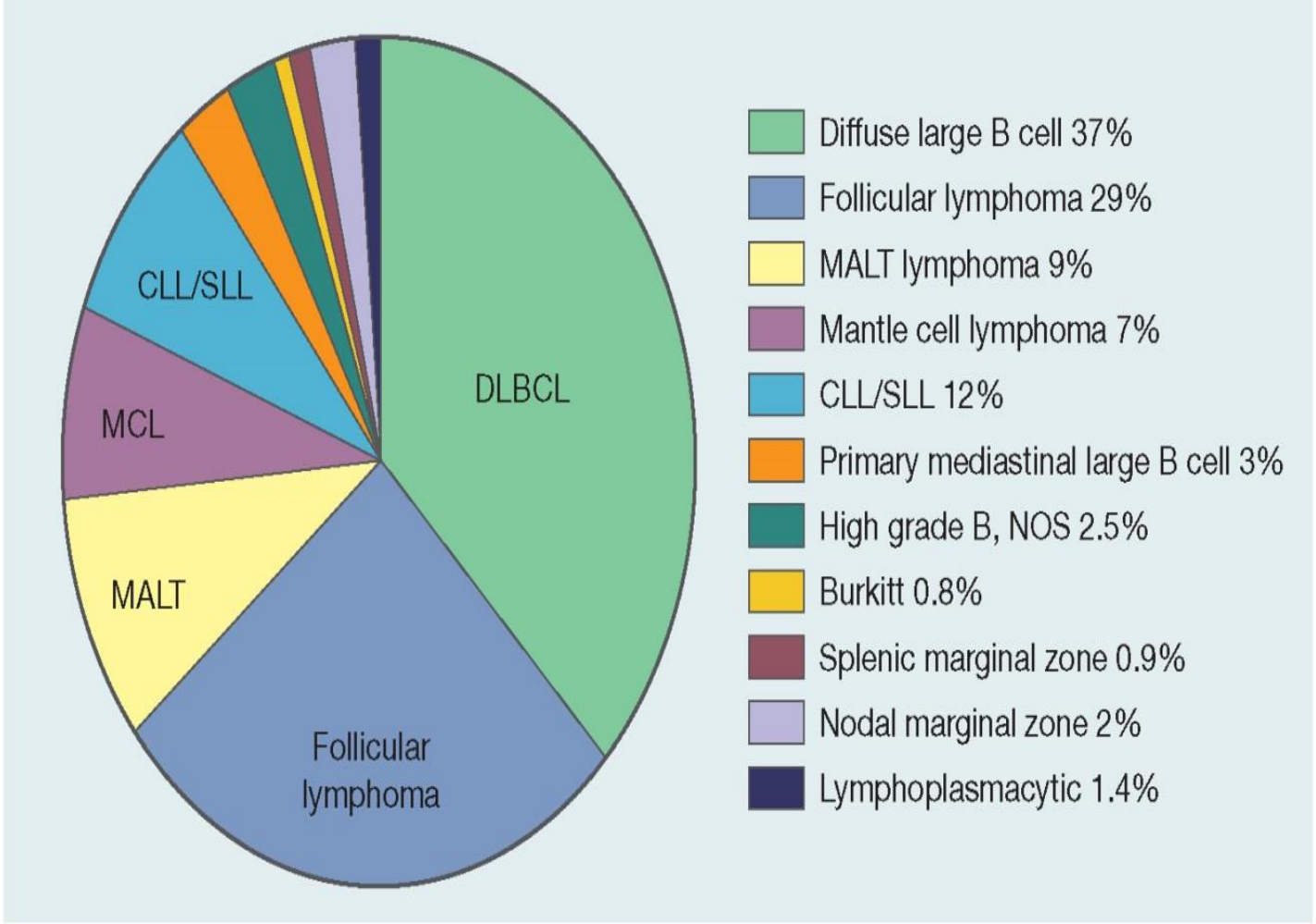


Figure 20.1 The relative frequencies of B-cell non-Hodgkin lymphomas. CLL, chronic lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; NOS, not otherwise specified; PMLBCL, primary mediastinal large B-cell lymphoma; SLL, small lymphocytic lymphoma.

Hoffbrand's Essential Haematology, Seventh Edition. By A. Victor Hoffbrand and Paul A. H. Moss.
Published 2016 by John Wiley & Sons Ltd.

Ne-Hodgkinovi limfomi

INCIDENCIJA I EPIDEMIOLOGIJA:

- broj bolesnika je u stalnom porastu (4%/g.)
- češća je u muškaraca (1.4:1)
- učestalost 12-16/100 000 stanovnika/g.
- povećan rizik kod onih s imunodeficijentnim stanjem (HIV, RA, imunosupresivna th.)

Ne-Hodgkinovi limfomi

ETIOLOGIJA:

- specifični etiološki agens je nepoznat
- sudjeluju razni faktori (poremećaj u regulaciji imunološkog sustava, Ebstein-Barr virus, HTLV-1, AIDS, H. pylori, virus hepatitisa C, herpes virus 8).

Ne-Hodgkinovi limfomi

PATOGENEZA I PATOFIZIOLOGIJA:

- limfomske stanice infiltriraju limfne čvorove, slezenu, koštanu srž te ponekad i druge organe
- infiltracija koštane srži uzrokuje insuficijenciju mijelopoeze (anemija, trombocitopenija, opetovane infekcije)

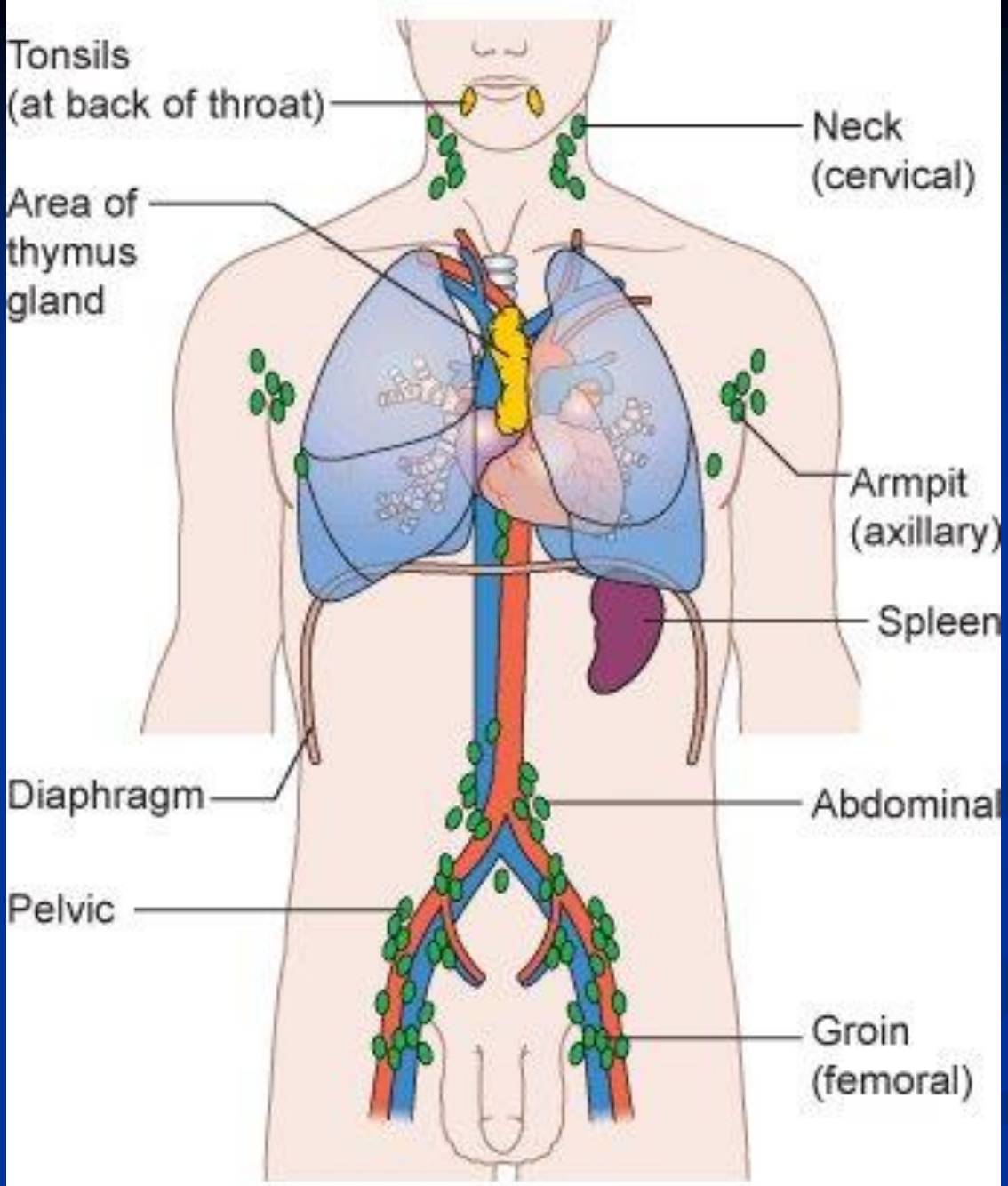
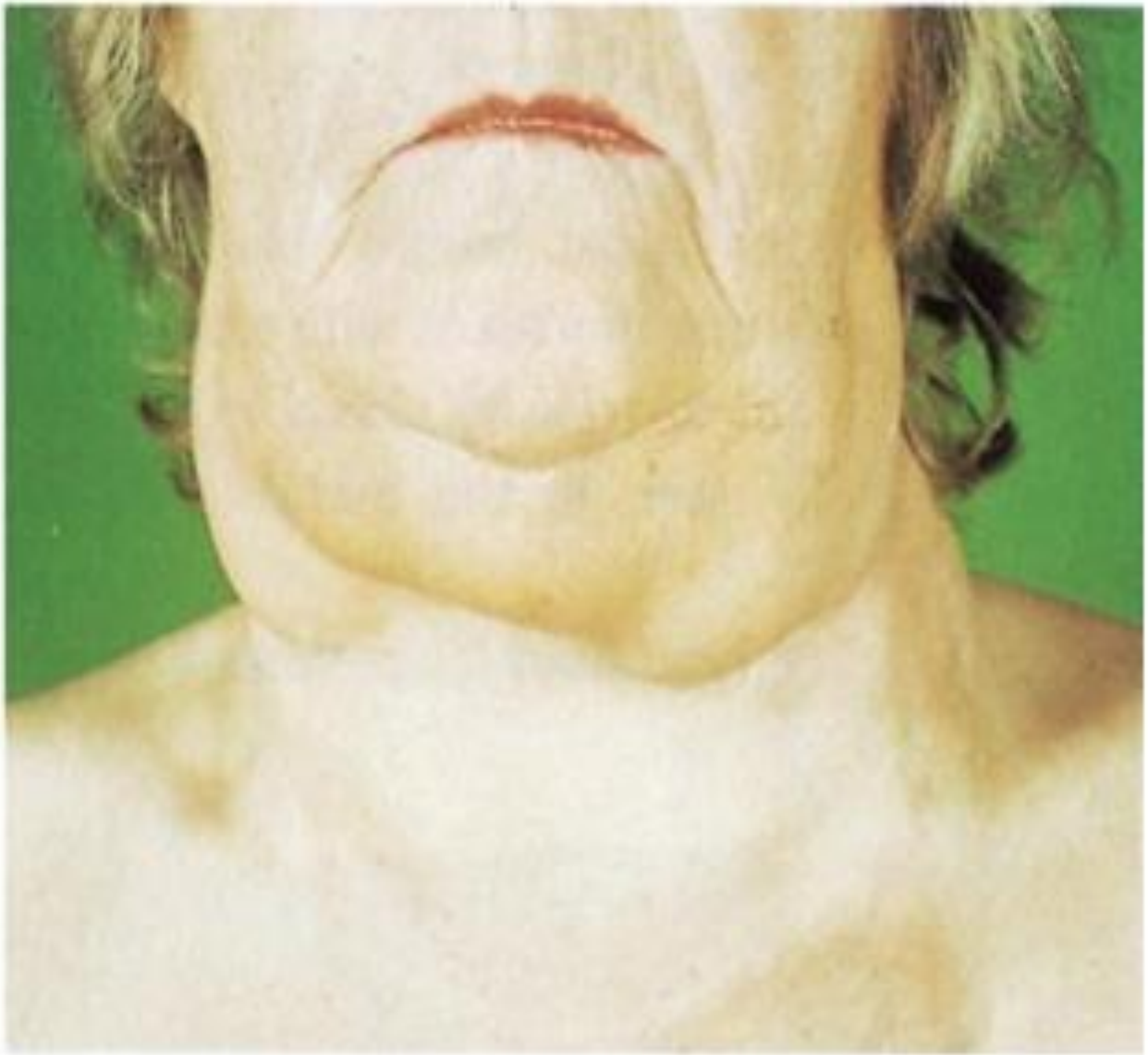


Diagram showing the position of the diaphragm and the lymph nodes NHL may develop in

Ne-Hodgkinovi limfomi

KLINIČKA SLIKA:

- pojava bezbolnih limfnih čvorova (oko 50%)
- ekstranodalna infiltracija (oko 25%)- u probavnom sustavu, infiltracija kože, pluća, kosti, SŽS
- hepato-splenomegalija (oko 30%)

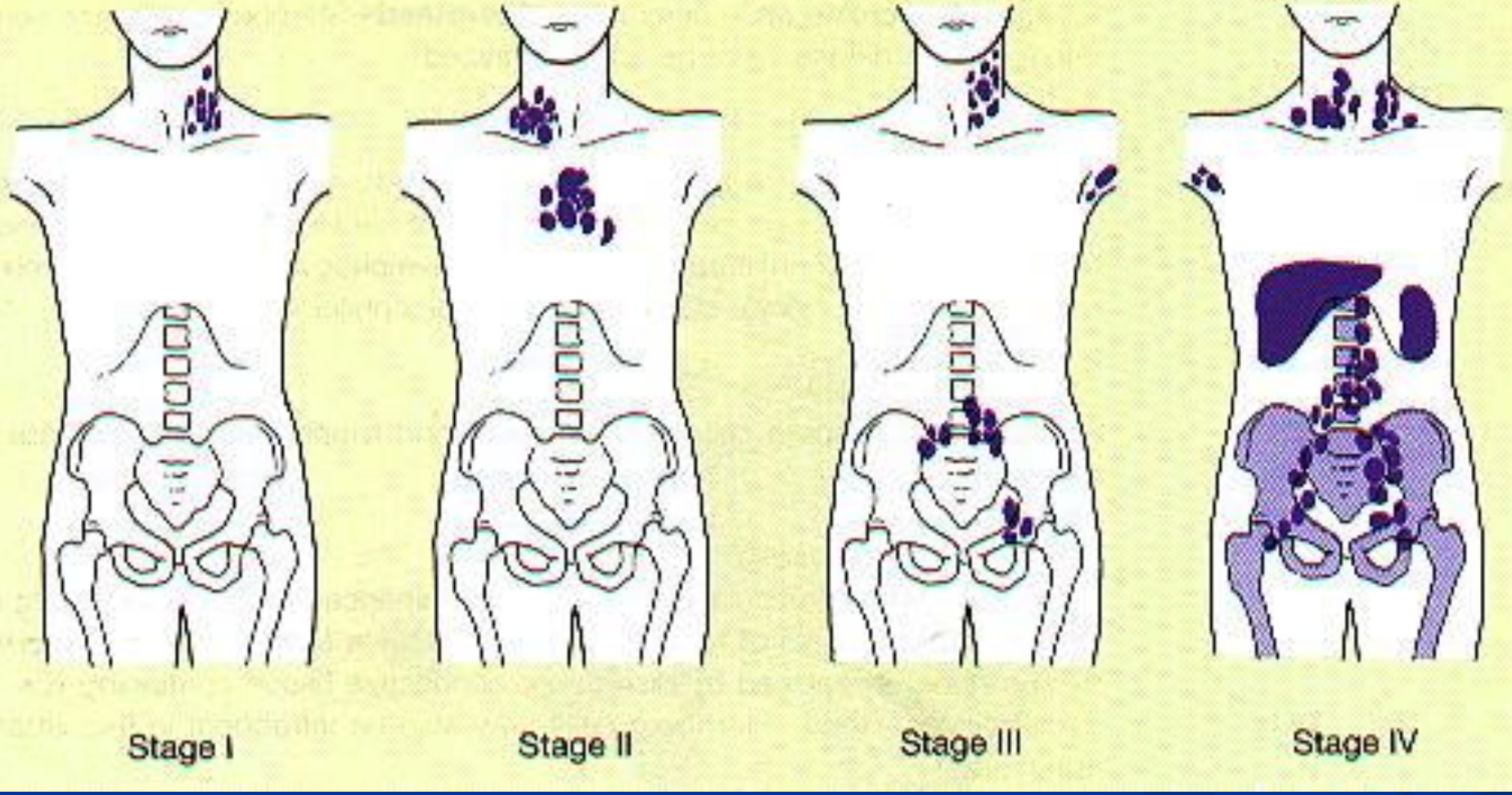


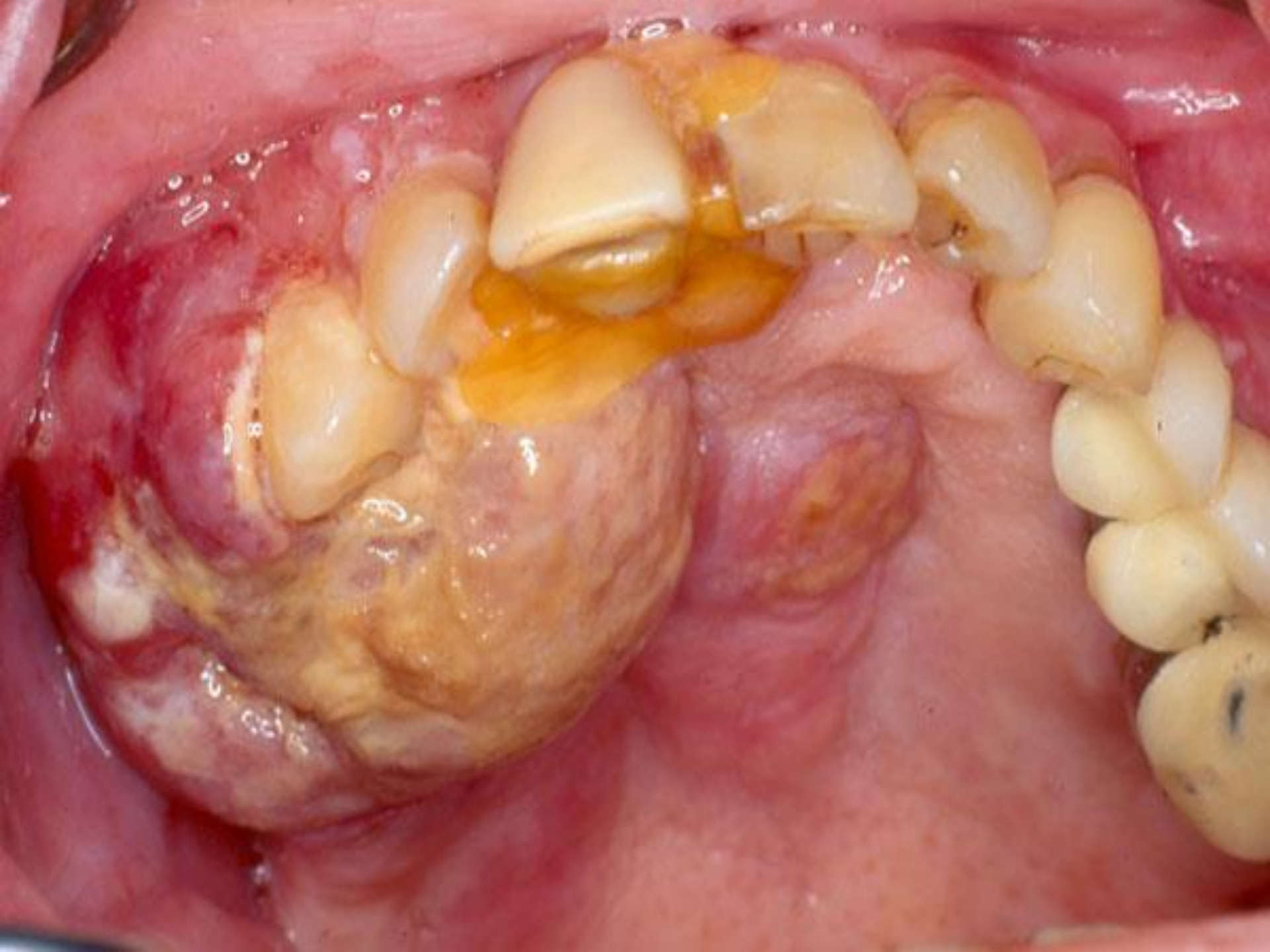
From: *Essential Haematology*, 6th Edn. © A. V. Hoffbrand & P. A. H. Moss. Published 2011 by Blackwell Publishing Ltd.

Ne-Hodgkinovi limfomi

KLINIČKA SLIKA:

- opći simptomi: povišena tjelesna temperatura, noćno znojenje, gubitak tjelesne težine
- *Indolentni oblici*: spori klinički tijek, diseminirana bolest
- *Agresivni oblik*: brži tijek, raniji smrtni ishod


Stage I
Stage II
Stage III
Stage IV



Ne-Hodgkinovi limfomi

DIFERENCIJALNA DIJAGNOZA:

- Kronična limfocitna leukemija
- infektivne bolesti (bakterije, virusi, infektivna mononukleoza, AIDS, toksoplazmoza), metastaza tm.

Ne-Hodgkinovi limfomi

DIJAGNOSTIKA:

- Biopsija limfnog čvora i koštane srži
- Imunotipizacija
- Citogenetika/molekularna dg.
- lab. nalazi (ubrzana SE, anemija,povišen LDH, hiperkalcemija)

Ne-Hodgkinovi limfomi

LIJEČENJE:

- Monoklonalna protutijela (rituksimab)
- Kemoterapija (CHOP)
- Radioterapija (lokalizirani oblici)
- Transplantacija koštane srži
- Kirurški (lokalizirani ekstranodularni agresivni)

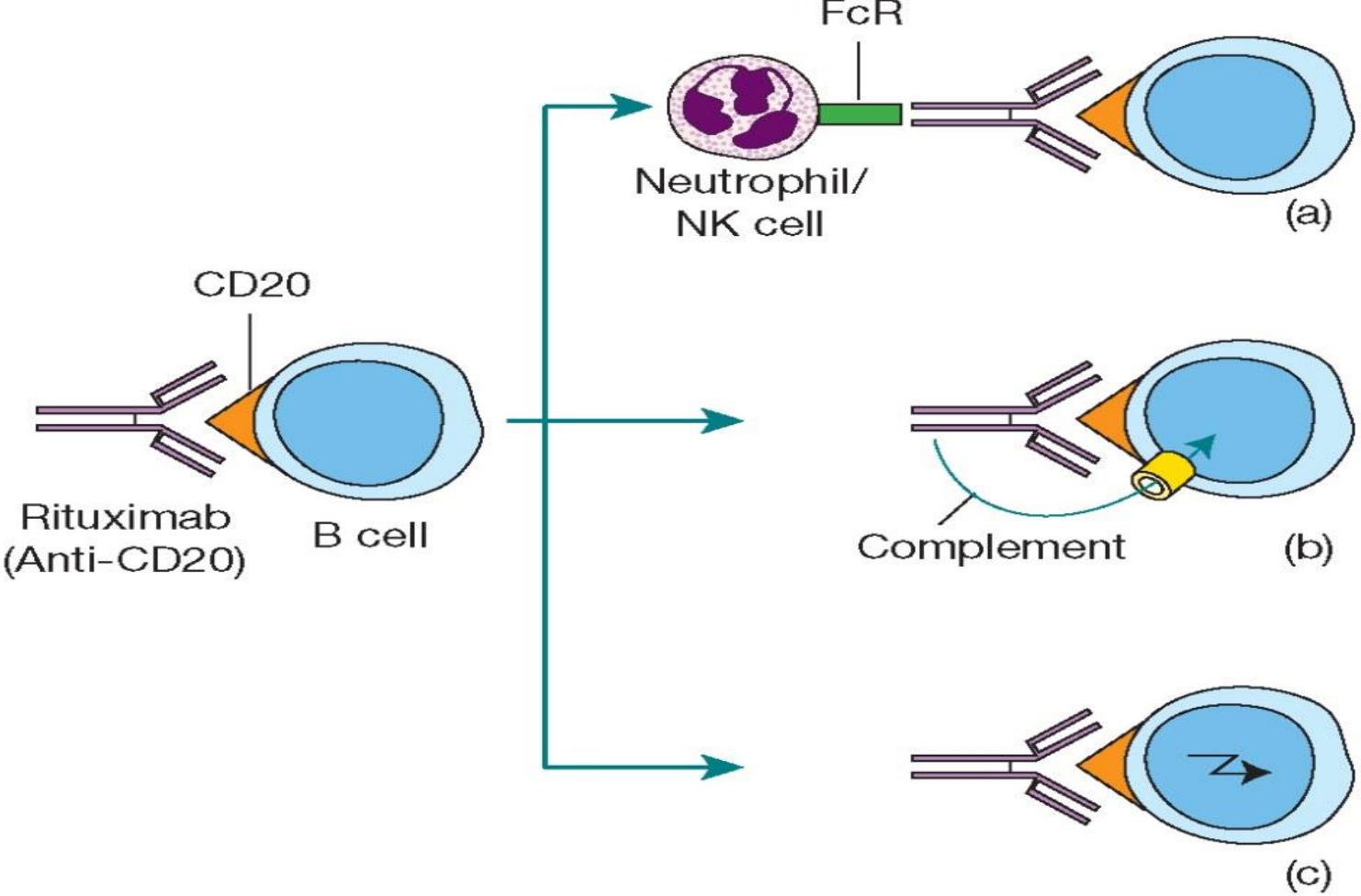


Figure 20.10 The potential mechanisms of action of rituximab. Rituximab binds to CD20 on the surface of B cells. It can elicit a number of effector mechanisms including: **(a)** antibody-dependent cell-mediated cytotoxicity; **(b)** complement-mediated lysis of tumour cells; and **(c)** direct apoptosis of the target cell.

Hoffbrand's Essential Haematology, Seventh Edition. By A. Victor Hoffbrand and Paul A. H. Moss.
Published 2016 by John Wiley & Sons Ltd.

Ne-Hodgkinovi limfomi

PROGNOZA:

- *Indolentni-* dobra prognoza (oko 10 g.)
- obično nisu izliječivi
- *Agresivni-* kraće preživljavanje ako se ne liječe
- u 30-60% se postiže izliječenje
- relapsi najčešće u prve 2 g.

Hodgkinov limfom

- Rijedak zloćudni tumor nepoznate etiologije (5-6/100 000 stanovnika)
- Zloćudna preobrazba prvenstveno zahvaća limfne čvorove
- Dijagnoza se postavlja na temelju karakterističnosti histološke slike uz obvezatan nalaz Reed-Sternbergovih stanica
- Bimomodalna krivulja (vršak u dobi od 30 i 60 godina)

Hodgkinov limfom

KLASIFIKACIJA:

- limfocitna predominacija
- nodularna skleroza
- miješana celularnost
- limfocitna deplecija

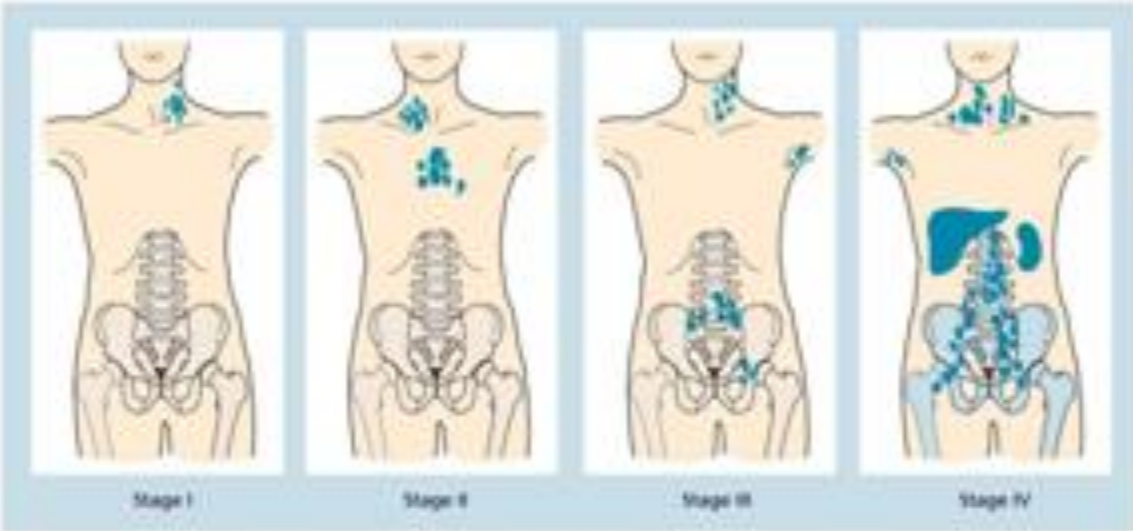


Figure 19.4 Staging of Hodgkin lymphoma. Stage I indicates node involvement in one lymph node area. Stage II indicates disease involving two or more lymph nodal areas confined to one side of the diaphragm. Stage III indicates disease involving lymph nodes above and below the diaphragm. Splenic disease is included in stage III but this has special significance (see below). Stage IV indicates involvement outside the lymph node areas and refers to diffuse or disseminated disease in the bone marrow, liver and other extranodal sites. NB. The stage number in all cases is followed by the letter A or B indicating the absence (A) or presence (B) of one or more of the following: unexplained fever above 38°C; night sweats; or loss of more than 10% of body weight within 6 months. Localized extranodal extension from a mass of nodes does not advance the stage but is indicated by the subscript E. Thus, mediastinal disease with contiguous spread to the lung or spinal theca would be classified as I_E. As involvement of the spleen is often a prelude to widespread haematogenous spread of the disease, patients with lymph node and splenic involvement are staged as III_S. Bulky disease (widening of the mediastinum by more than one-third, or the presence of a nodal mass >10cm in diameter) is relevant to therapy at any stage.

Hodgkinov limfom

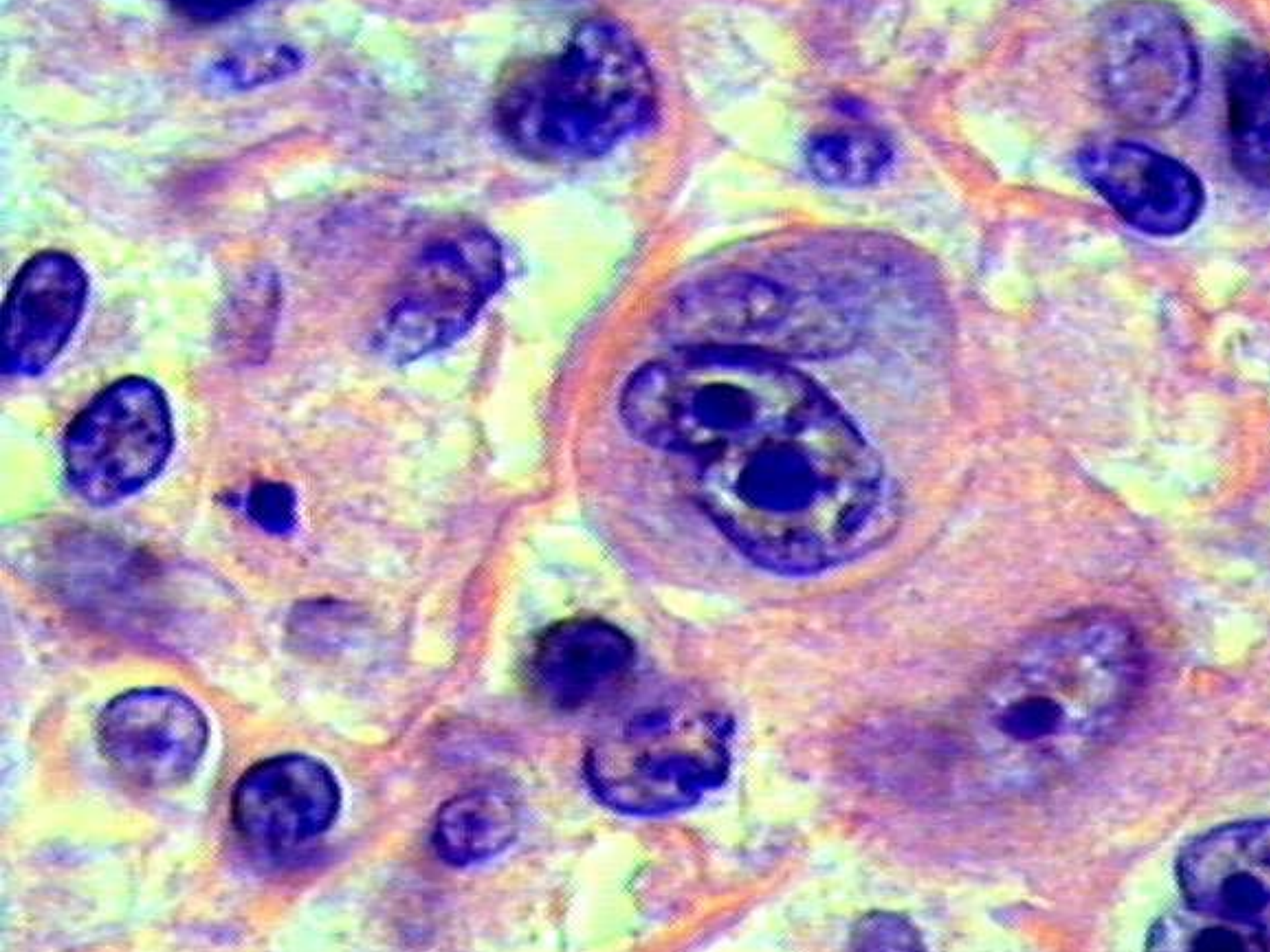
KLINIČKA SLIKA:

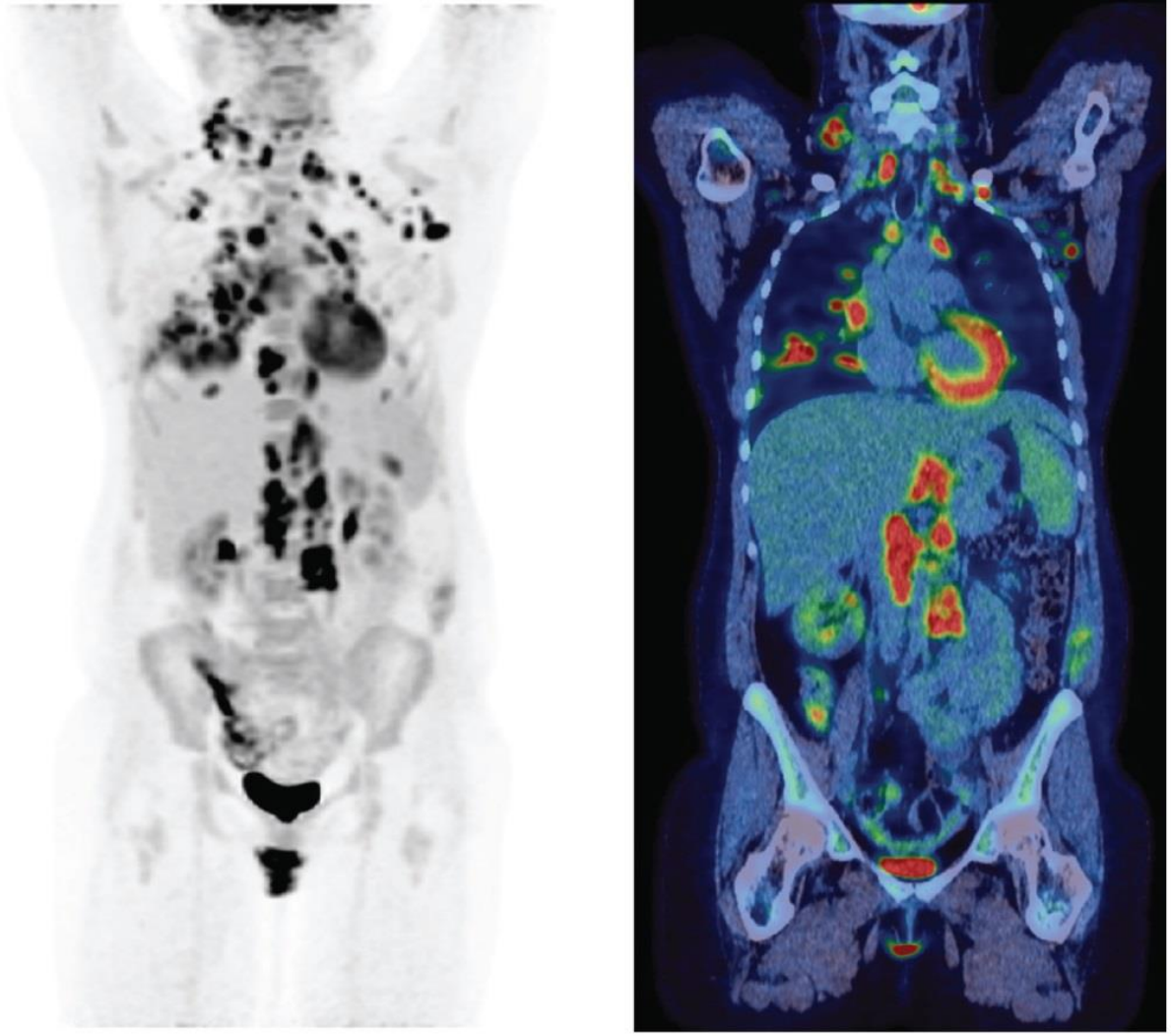
- povećan limfni čvorovi (“paketi” na vratu, pazusima, preponi, medijastinumu, retroperitonealno)
- povišena tjelesna temperatura, znojenje, mršavljenje
- jak svrbež kože
- bol u zahvačenim područjima nakon uzimanja alkohola

Hodgkinov limfom

DIJAGNOZA:

- lab. nalazi (ubrzana SE, leukocitoza s granulocitozom, eozinofilija, monocitoza, limfopenija, anemija, povišeni su serumski Cu, haptoglobin, alkalna fosfataza, poremećaj stanične imunosti)
- histološka dijagnostika (biopsija limfnog čvora- Reed Sternberg stanice)





(a) (b)

Figure 19.6 Hodgkin lymphoma. Staging PET/CT: 35-year-old female who had disease above and below the diaphragm at presentation. **(a)** Coronal PET image shows multiple foci of uptake above and below the diaphragm. **(b)** Coronal fused PET/CT scan image shows multiple foci of uptake above and below the diaphragm corresponding to nodes, spleen and lung nodules. PET stage IV. Source: Courtesy Dr Thomas Wagner and the Department of Nuclear Medicine, Royal Free Hospital, London.

Hoffbrand's Essential Haematology, Seventh Edition. By A. Victor Hoffbrand and Paul A. H. Moss.
Published 2016 by John Wiley & Sons Ltd.

Hodgkinov limfom

LIJEČENJE:

- Radioterapija (tehnika plašta)
- kemoterapija (MOPP, ABVD protokoli), može se postići remisija u 80% bolesnika
- autologna transplantacija koštane srži

Hodgkinov limfom

PROGNOZA:

- veliki je postotak kompletnih remisija (oko 85%) nakon primjenjene terapije
- pojava sekundarnih malignoma i leukemija, naročito nakon radioterapije (pluća, koštani, želučani, mekih tkiva) pojavljuju se isključivo u polju zračenja

POREMEĆAJI PLAZMA STANICA

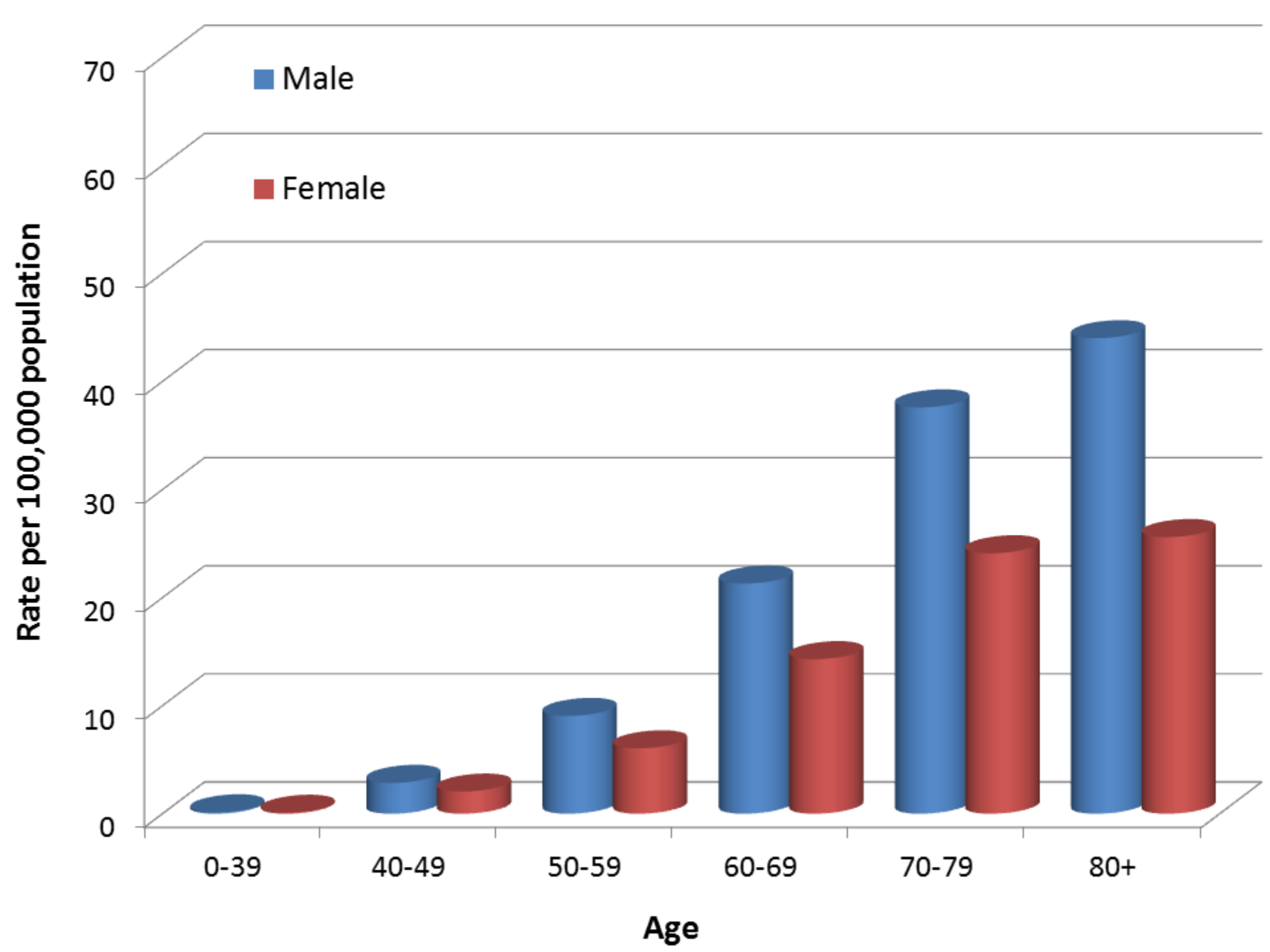
- Poliklonski: autoimune bolesti
  kronične infekcije
  kronične bolesti jetre

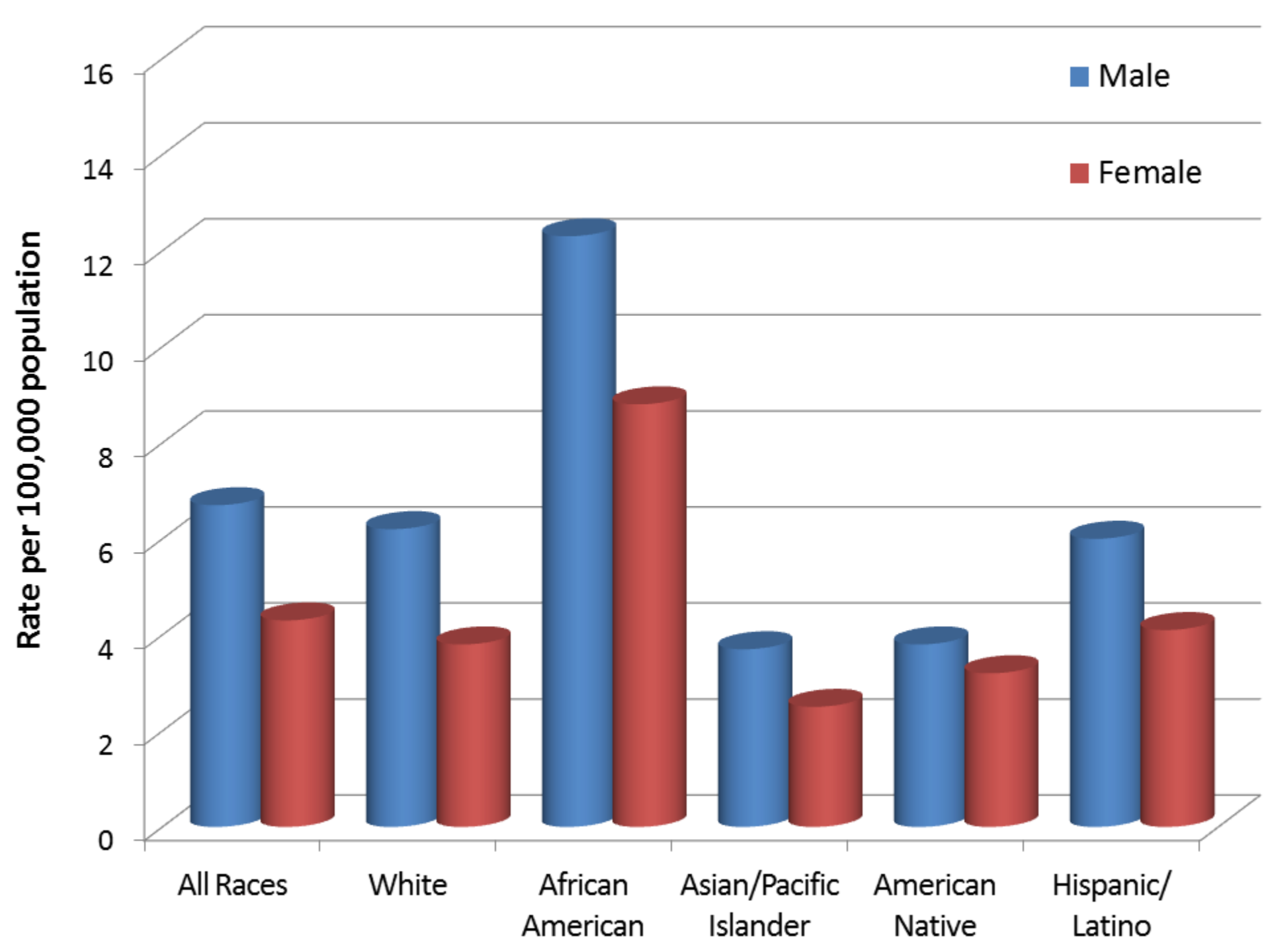
- Monoklonski: multipli mijelom
  makroglobulinemijaWaldenstrom

Plazmocitom (multipli mijelom)

DEFINICIJA:

- Zloćudna bolest plazma stanica obilježena stvaranjem M-proteina (monoklonski protein)
- Čini oko 10% hematoloških malignoma
- Pojavljuje se u starijoj životnoj dobi (medijan 70 godina života)
- Samo je 2% mlađe od 40 godina


Male
Female
70
60
50
40
30
20
10
0
Rate per 100,000 population
0-39
40-49
50-59
60-69
70-79
80+
Age


Male
Female
Rate per 100,000 population
16
14
12
10
8
6
4
2
0
All Races
White
African American
Asian/Pacific Islander
American Native
Hispanic/ Latino

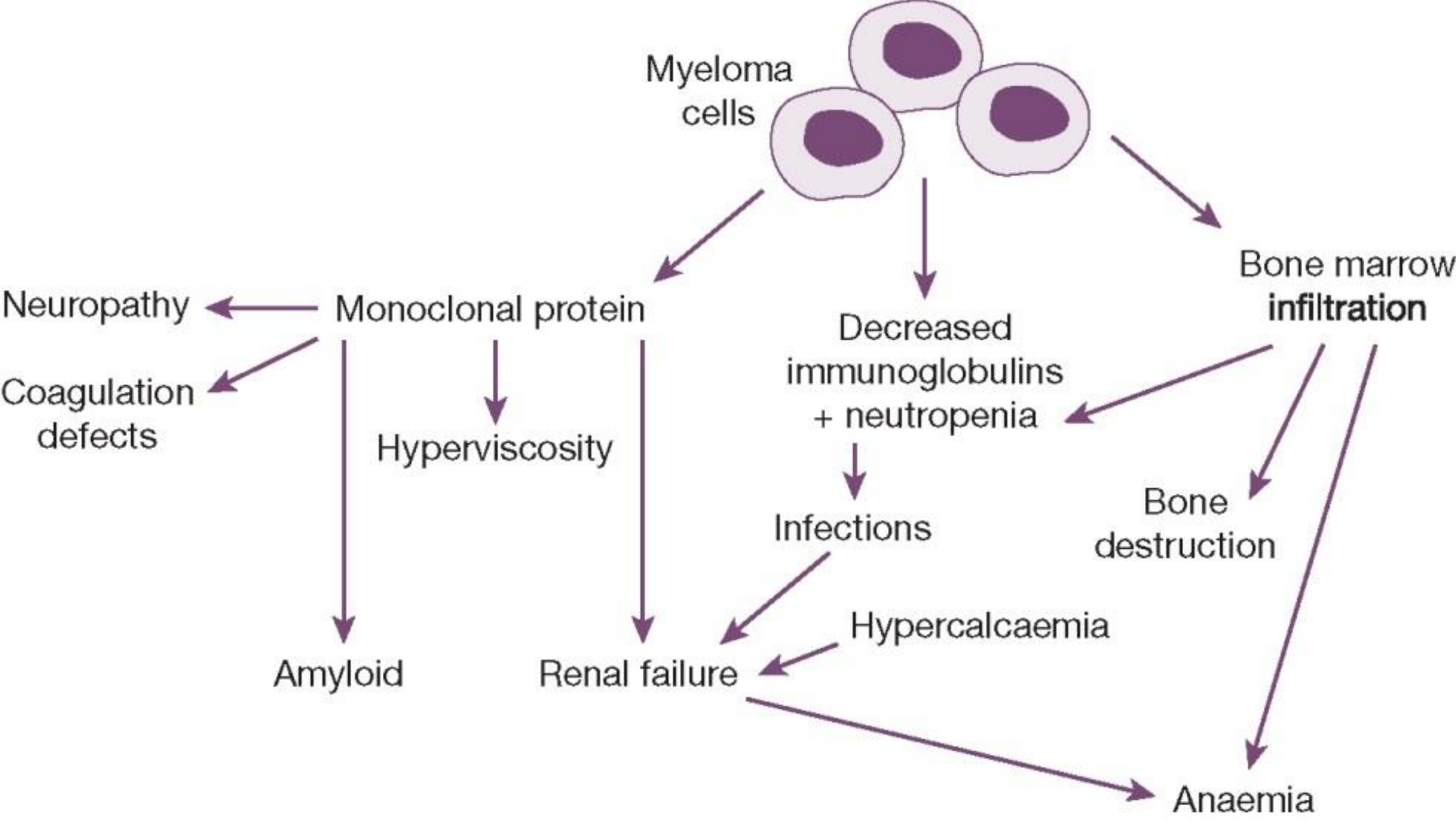


Figure 21.4 The pathogenesis of the clinical features of myeloma.

Hoffbrand's Essential Haematology, Seventh Edition. By A. Victor Hoffbrand and Paul A. H. Moss. Published 2016 by John Wiley & Sons Ltd.

Plazmocitom (multipli mijelom)

KLINIČKA SLIKA:

- U početnom stadiju ne izaziva nikakvih tegoba
- Bolovi u kostima
- Simptomi anemije
- Zatajivanje bubrega
- Infekcije
- Hiperviskozni sindrom
- Krvarenja

Plazmocitom (multipli mijelom)

DIJAGNOZA:

- klinička slika
- ubrzana SE
- Monoklonalni imunoglobulin u ELF > 30g/L
- Izlučivanje >1,0g/24h kapa ili lambda lakih lanaca u urinu
- U koštanoj srži > 10% plazma stanica
- Litičke lezije u kostima

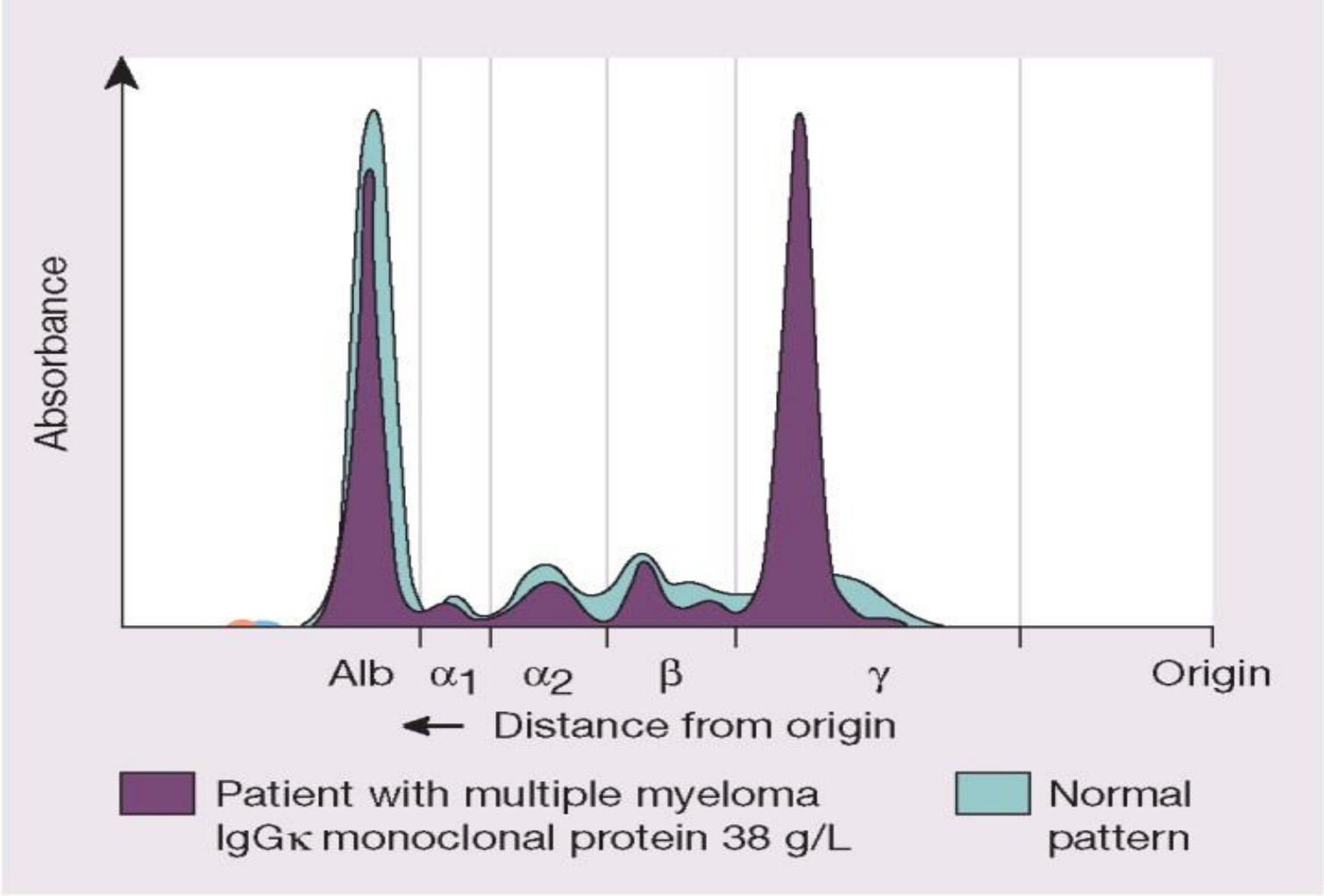
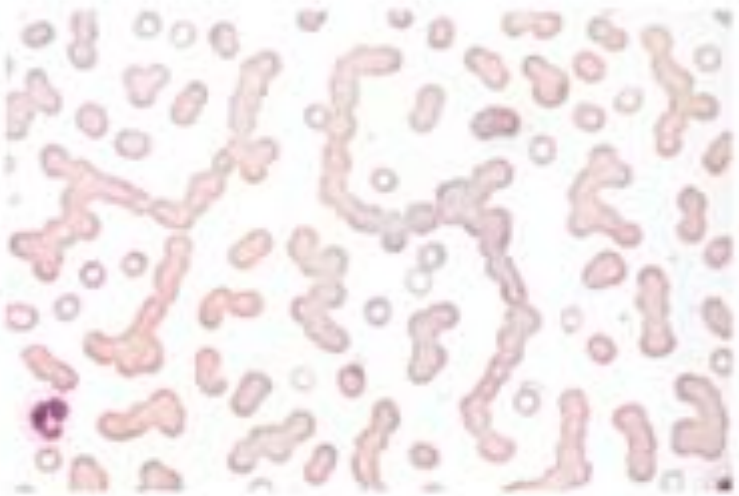


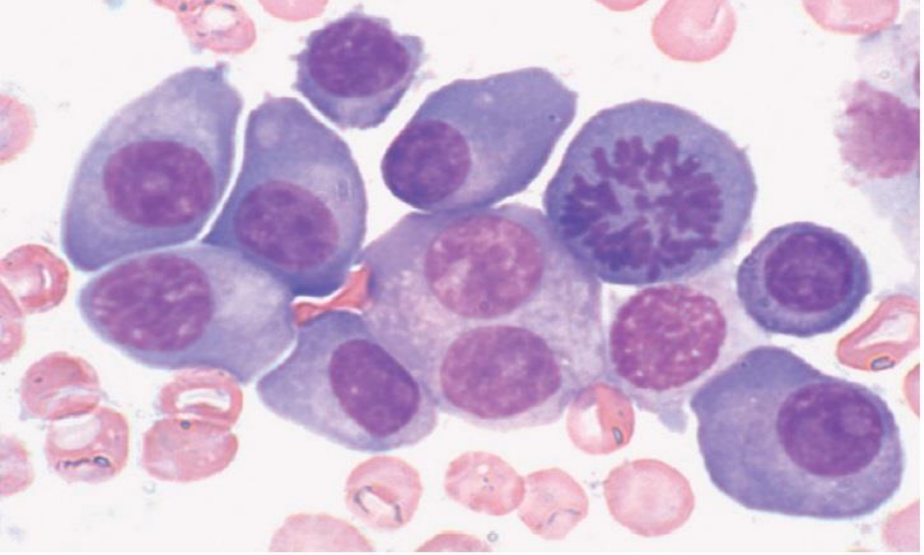
Figure 21.1 Serum protein electrophoresis in multiple myeloma showing an abnormal paraprotein in the γ-globulin region with reduced levels of background β- and γ-globulins.

Hoffbrand's Essential Haematology, Seventh Edition. By A. Victor Hoffbrand and Paul A. H. Moss.
Published 2016 by John Wiley & Sons Ltd.

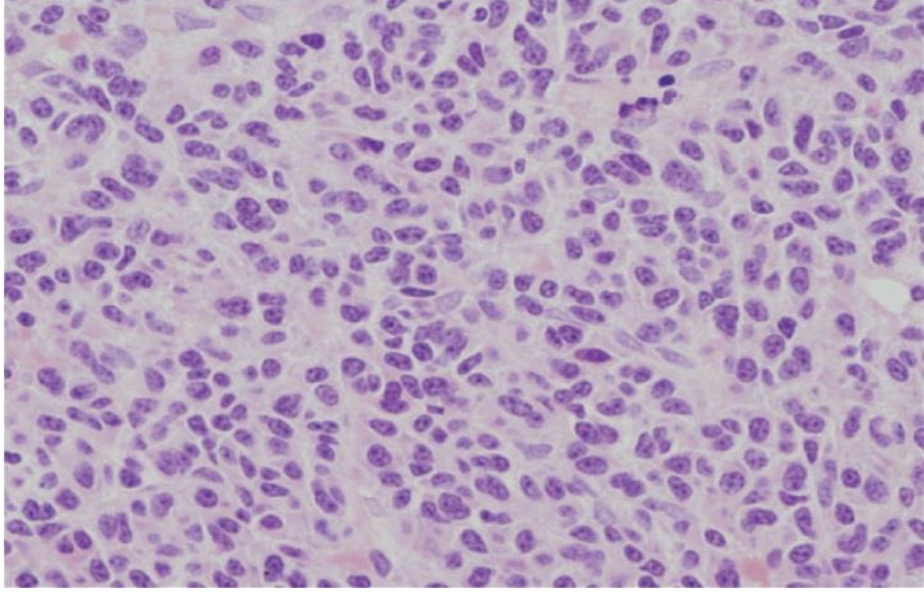


From: Essential Haematology, 6th Edn, (D A. V. Hoffbrand & P. A. H. Moss. Published 2011 by Blackwell Publishing Ltd.

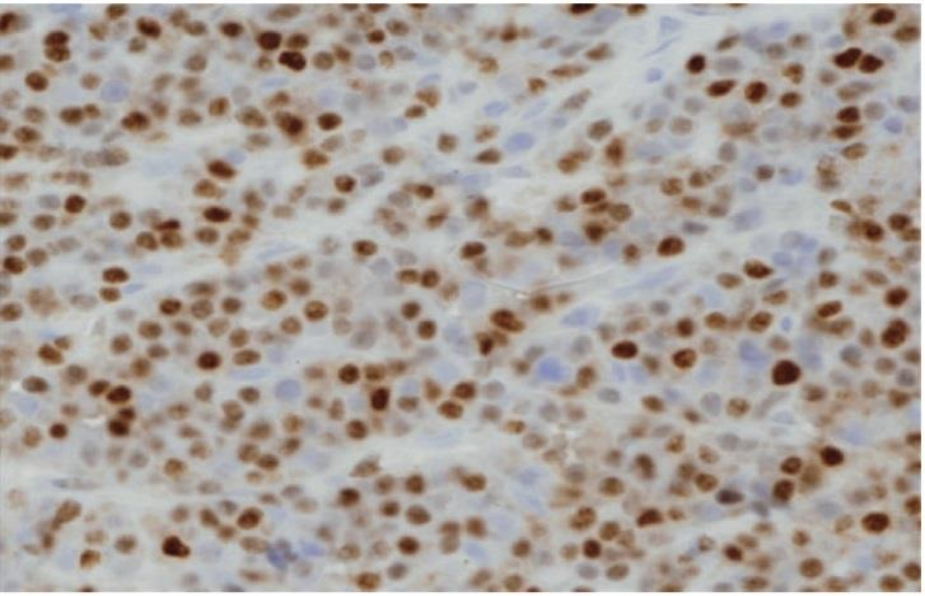
Figure 21.5 The peripheral blood film in multiple myeloma showing Rouleaux formations.



(a)



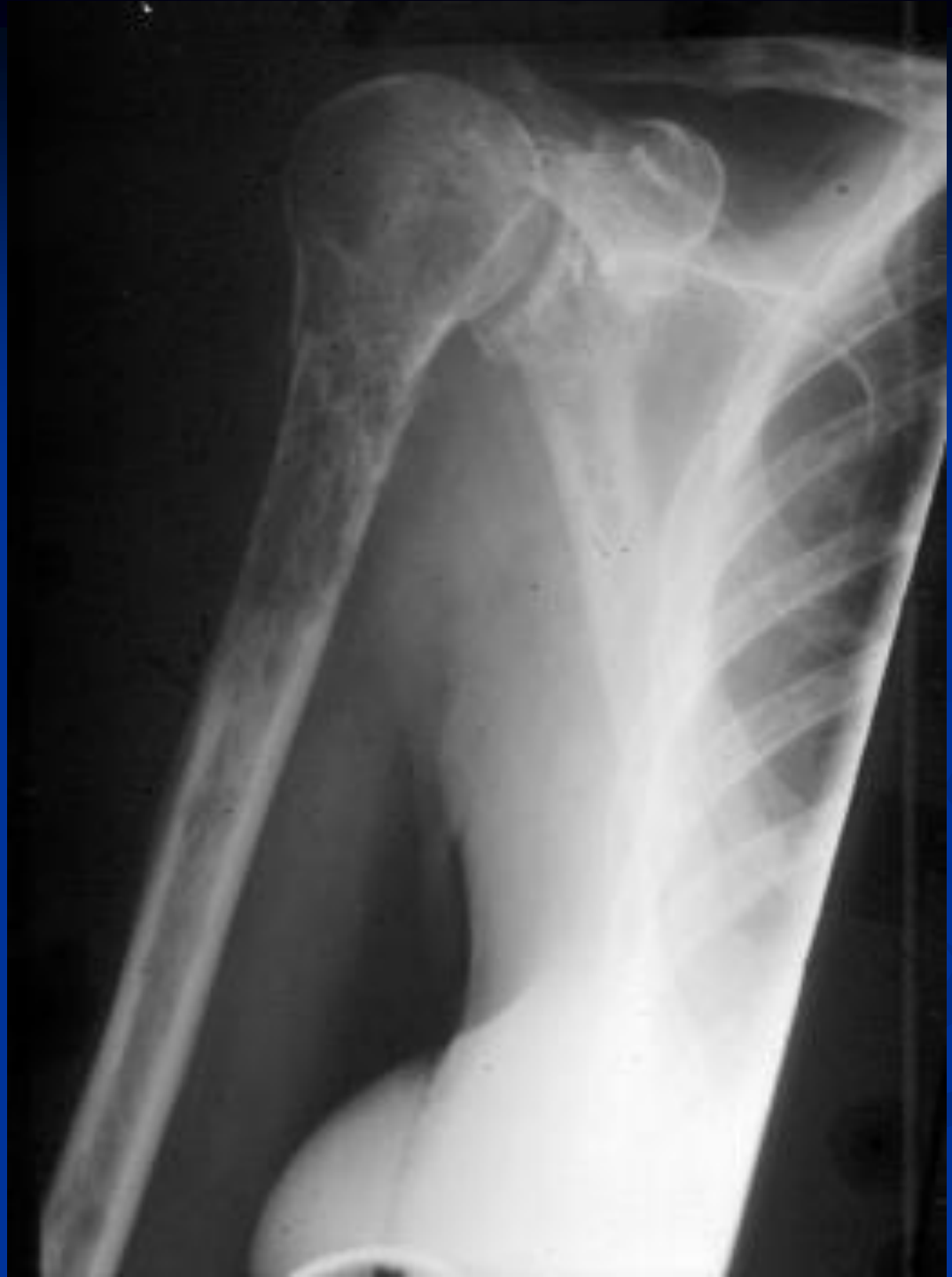
(b)

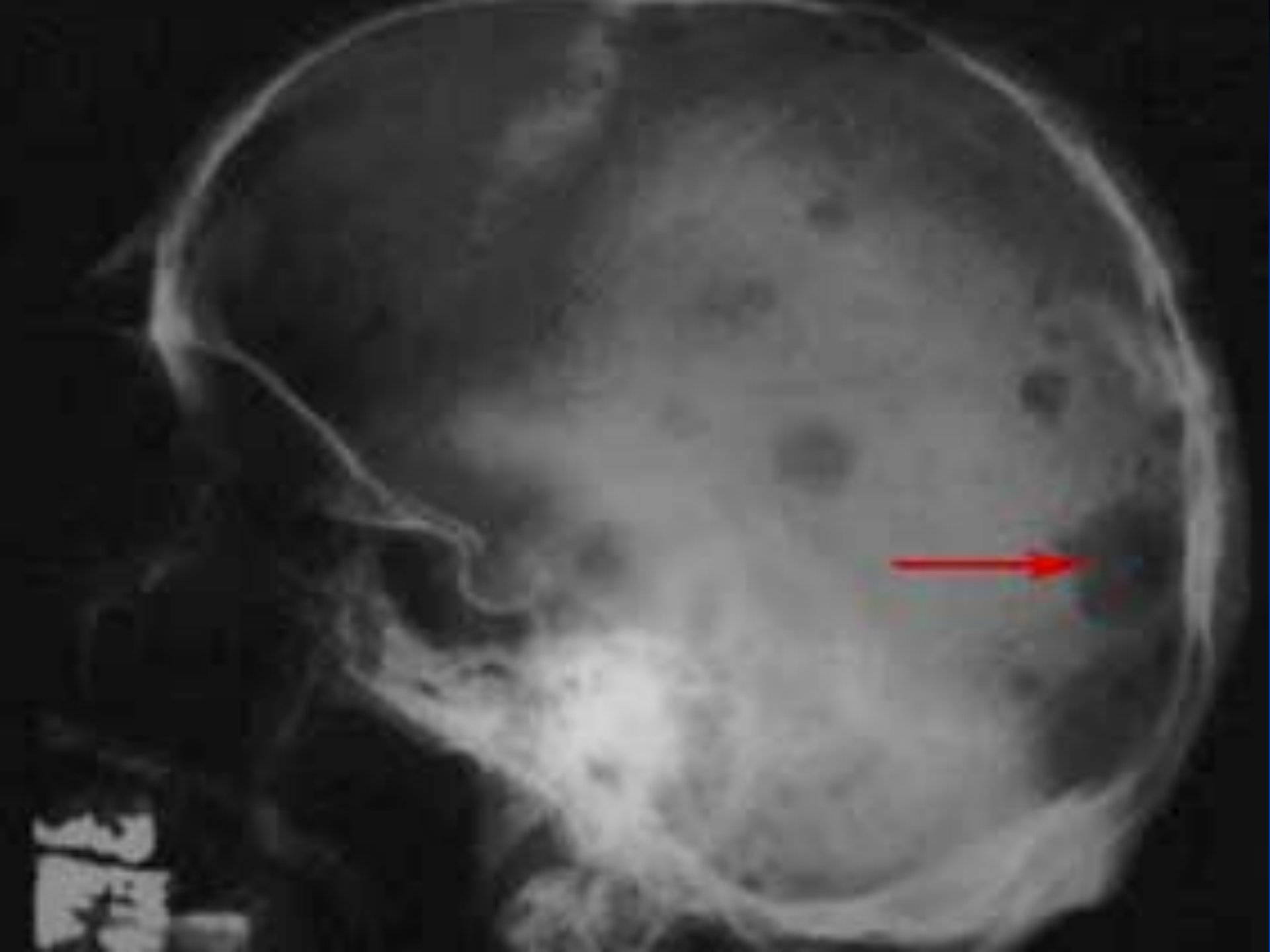


(c)

Figure 21.2 **(a)** The bone marrow in multiple myeloma showing large numbers of plasma cells, with many abnormal forms. **(b)** Low-power view showing sheets of plasma cells replacing normal haemopoietic tissue. **(c)** Immunohistochemical staining of the bone marrow in myeloma with antibody to CD138 revealing extensive numbers of plasma cells.

Hoffbrand's Essential Haematology, Seventh Edition. By A. Victor Hoffbrand and Paul A. H. Moss.
Published 2016 by John Wiley & Sons Ltd.





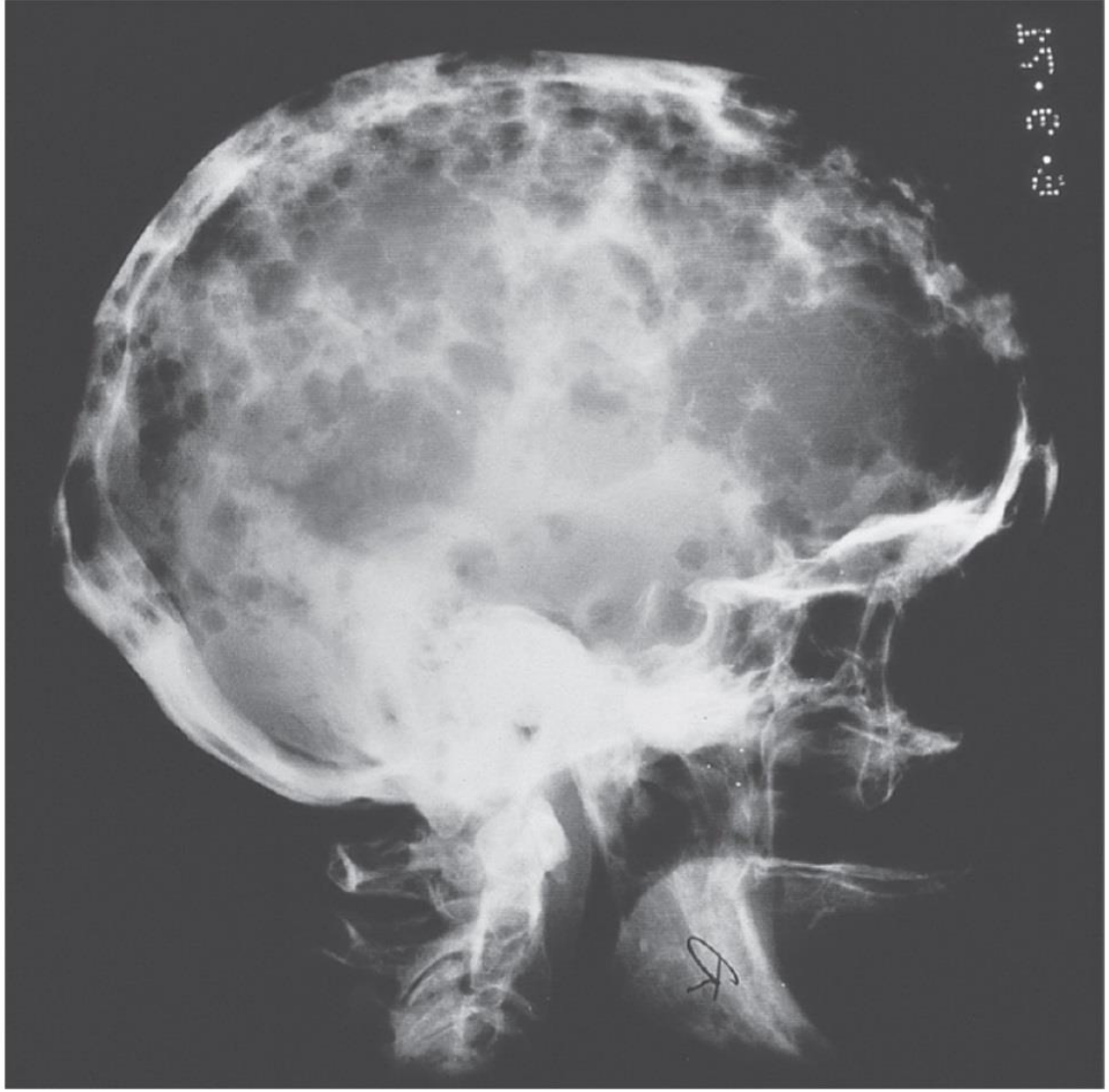
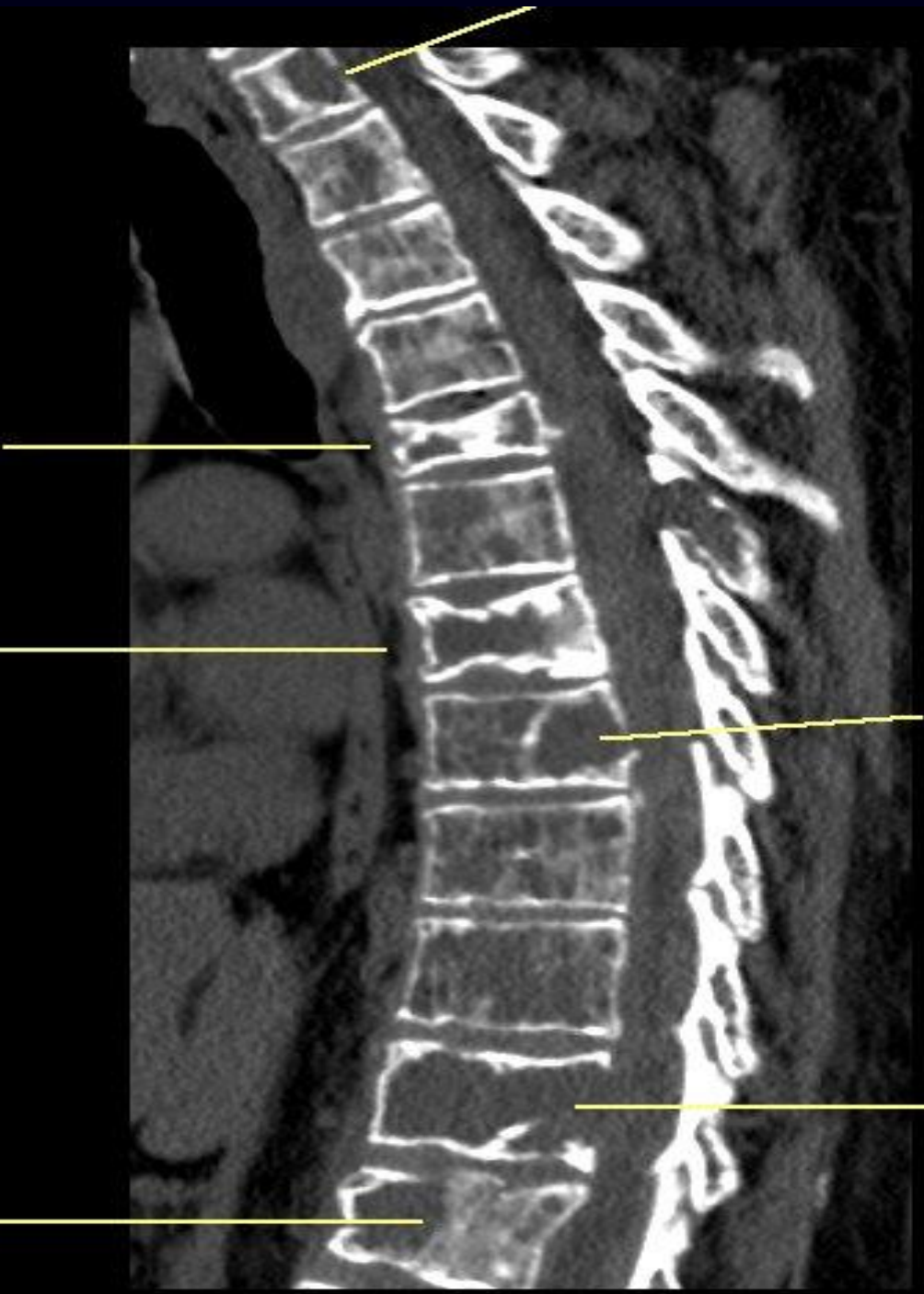


Figure 21.8 Skull X-ray in multiple myeloma showing many 'punched-out' lesions.

Hoffbrand's Essential Haematology, Seventh Edition. By A. Victor Hoffbrand and Paul A. H. Moss.
Published 2016 by John Wiley & Sons Ltd.



advanced myeloma
of the spine
with lytic lesions
and compression
fractures

ODREĐIVANJE STADIJA BOLESTI

- Procjena litičke lezije u kostima
  Razina M-proteina u serumu
  Koncentracija hemoglobina
  Koncentracija kalcija u serumu
  Bubrežna disfunkcija

- Koncentracija $beta_2$ mikroglobulina
  Koncentracija albumina u serumu

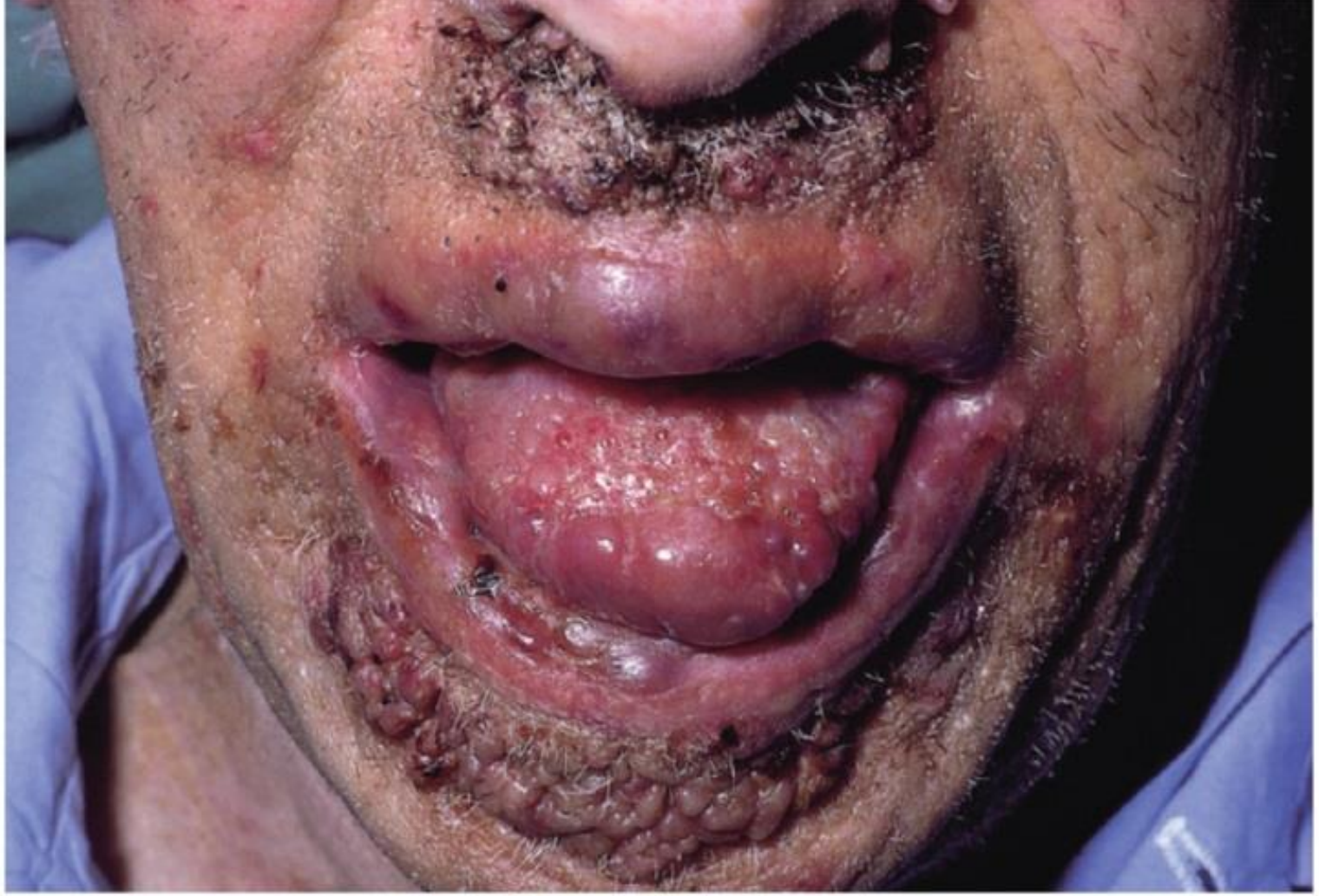


Figure 21.13 Multiple myeloma: the tongue and lips are enlarged because of nodular and waxy deposits of amyloid.

Hoffbrand's Essential Haematology, Seventh Edition. By A. Victor Hoffbrand and Paul A. H. Moss.
Published 2016 by John Wiley & Sons Ltd.

Plazmocitom (multipli mijelom)

LIJEČENJE:

1. Mijelosupresijsko
2. Transplantacija autologne koštane srži
3. Radioterapija
4. Potporno liječenje

Plazmocitom (multipli mijelom)

PROGNOZA:

- Medijan preživljenja je 3 godine
- 35% liječenih živi dulje od 5 godine
- Bolesnici s izraženom bubrežnom insuficijencijom žive samo nekoliko mjeseci
- Loši prognostički čimbenici su teška anemija, sniženi serumski albumini, izrazita Bence-Jonesova proteinurija, te povišeni beta$_2$-mikroglobulinemija

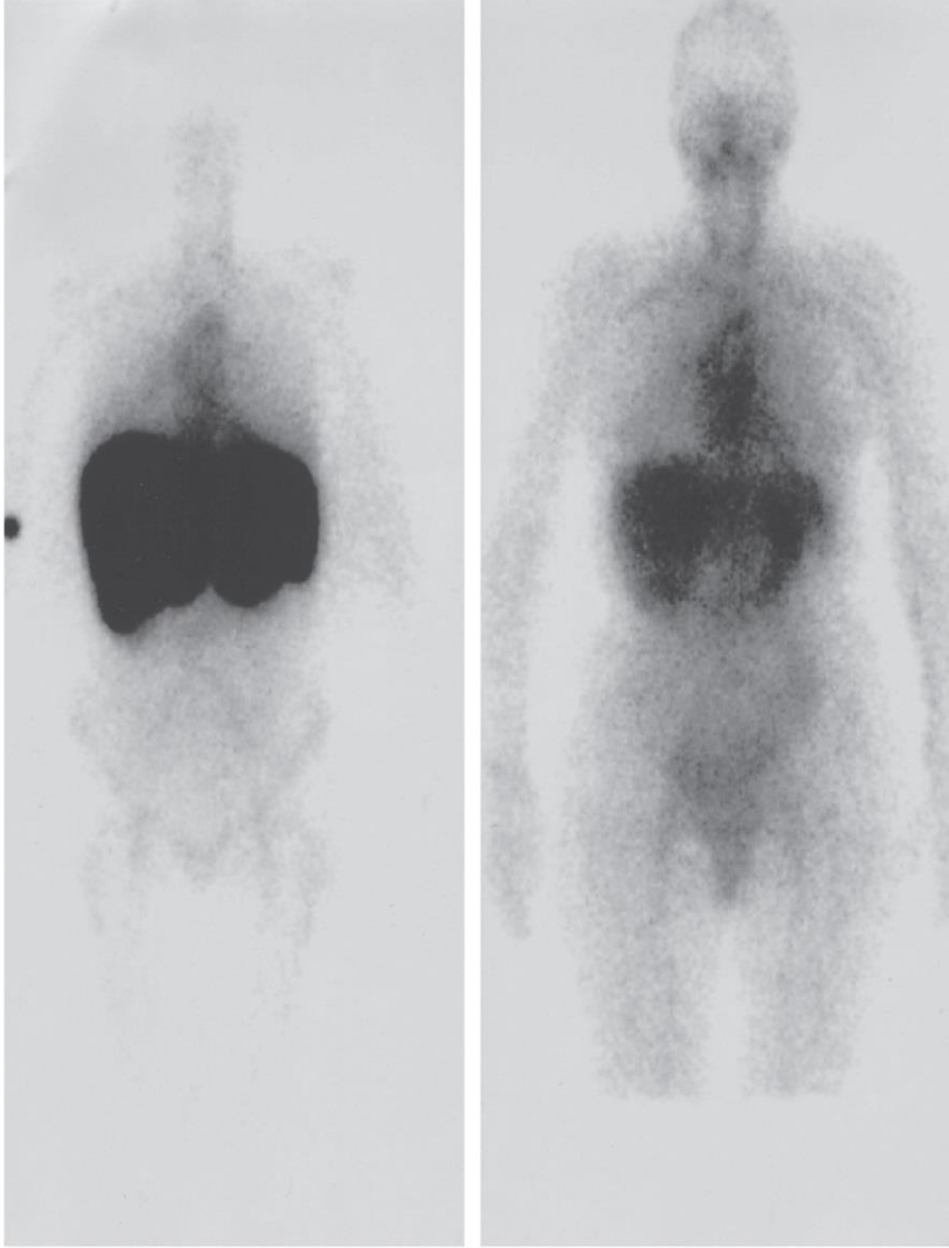


Figure 21.14 Serial anterior whole body ^{123}I-labelled serum amyloid P component (SAP) scans of a 52-year-old woman who presented with renal failure resulting from systemic AL amyloidosis. **(a)** The initial scan demonstrates a large amyloid load with hepatic, splenic, renal and bone marrow deposits. The underlying plasma cell dyscrasia responded to high-dose melphalan followed by autologous stem cell rescue. **(b)** Follow-up SAP scintigraphy 3 years after chemotherapy showed greatly reduced uptake of tracer indicating substantial regression of her amyloid deposits. Source: Courtesy of Professor P.N. Hawkins, National Amyloidosis Centre, Royal Free Hospital, London.

Hoffbrand's Essential Haematology, Seventh Edition. By A. Victor Hoffbrand and Paul A. H. Moss.
Published 2016 by John Wiley & Sons Ltd.

Periodontal Manifestations

- The gingivae appears congested and edematous and may bleed spontaneously because of hyperviscosity and hypertension.
- Gingival enlargement may be seen.